

Topics in Heterocyclic Chemistry 40

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Wim Dehaen

Vasiliy A. Bakulev *Editors*

Chemistry of 1,2,3-triazoles

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Topics in Heterocyclic Chemistry

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The series Topics in Heterocyclic Chemistry presents critical reviews on present and future trends in the research of heterocyclic compounds. Overall the scope is to cover topics dealing with all areas within heterocyclic chemistry, both experimental and theoretical, of interest to the general heterocyclic chemistry community.

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Wim Dehaen • Vasiliy A. Bakulev

Editors

Chemistry of 1,2,3-triazoles

With contributions by

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R. Ballesteros-Garrido • N. Belskaya • T. Beryozkina •
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ISSN 1861-9282

ISBN 978-3-319-07961-5

DOI 10.1007/978-3-319-07962-2

Springer Cham Heidelberg New York Dordrecht London

ISSN 1861-9290 (electronic)

ISBN 978-3-319-07962-2 (eBook)

Library of Congress Control Number: 2014951200

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Preface

The chemistry of 1,2,3-triazoles has been an important topic in heterocyclic chemistry since the first such heterocycles were prepared in the nineteenth century by von Pechmann (1888). Publications on triazoles have increased steadily ever since but there has recently been a remarkable additional interest due to the CuAAC (copper-catalyzed acetylene/azide cycloaddition) discovered by Meldal and Sharpless and related azide cycloaddition reactions, leading to a surge of publications and new applications for triazoles. A volume in this series of “Topics in Heterocyclic Chemistry” was already devoted to “Click Triazoles” (2012), edited by Janez Kosmrlj, but certainly not all parts of the versatile 1,2,3-triazole chemistry were covered at that time and this new volume can be seen as complementary.

In the first chapter, we reviewed the rearrangements and ring transformations of 1,2,3-triazoles. Especially the denitrogenative ring transformations enjoy great current interest. Natalya Belskaya et al. cover the progress in the area of the chemistry of the isomeric *2H*-1,2,3-triazoles (see chapter “Synthesis of *2H*-1,2,3-Triazoles”). Besides the synthetic procedures towards triazoles related to CuAAC, many others exist and Nazary Pokhodylo gives an overview of the multicomponent and domino processes leading to 1,2,3-triazoles (see chapter “Biological Properties of *1H*-1,2,3- and *2H*-1,2,3-Triazoles”). Quaternization of the triazole nucleus leads to interesting materials and this is reflected in two chapters by Jurgen Liebscher and Zekarias Jakob on one hand and Jezus Aizpura et al. on the other hand, who deal, respectively, with triazolium ionic liquids (see chapter “Chemistry of 1,2,3-Triazolium Salts”) and mesoionic and carbene derivatives of triazole (see chapter “Mesoionic 1,2,3-Triazoles and 1,2,3-Triazole Carbenes”). Vitor Ferreira et al. are giving an overview of the many biological properties of 1,2,3-triazole derivatives (see chapter “Multicomponent and Domino Reactions Leading to 1,2,3-Triazoles”), and finally there is a survey by Belen Abarca et al. about 1,2,3-triazoles fused to aromatic rings (see chapter “1,2,3-Triazoles Fused to Aromatic Rings”).

Our aim in editing this book was to show the versatility of the chemistry of the 1,2,3-triazole ring, and the many applications of this heterocycle in different fields ranging from medicinal chemistry, organocatalysis, development of new reaction

media, structural chemistry or in organic synthesis as starting materials. We thank all authors and the people at Springer for their essential efforts to realize this volume.

Leuven, Belgium
Yekaterinburg, Russia
May 2014

Wim Dehaen
Vasiliy A. Bakulev

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Top Heterocycl Chem (2015) 40: 1–50
DOI: 10.1007/7081_2014_131
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Published online: 25 June 2014

Thermal Rearrangements and Transformations of 1,2,3-Triazoles

Vasiliy Bakulev, Wim Dehaen, and Tetyana Beryozkina

Abstract This chapter concentrates on the thermal rearrangements and transformations of 1,2,3-triazoles. It also contains data on the ring-chain tautomerism of 1,2,3-triazoles and the substituent effect on the position of the equilibrium between diazoimines and 1,2,3-triazoles. The main part of this review has been devoted to transition-metal-catalyzed denitrogenative transformation of 1,2,3-triazoles.

Keywords 1-Tosyl-1,2,3-triazoles · Diazoimines · Flash vacuum pyrolysis · Rearrangements · Rhodium catalysts · Transformations

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Abbreviations

(<i>R</i>)-{NTV} ₄	αR - α -(isopropyl)-1,3-dioxo-2H-benz[de]isoquinoline-2-acetato
(<i>S</i>)-{NTTL} ₄	αS - α -(tert-butyl)-1,3-dioxo-2H-benz[de]isoquinoline-2-acetato
1,2-DCE	1,2-Dichloroethane
Alk	Alkyl
BDPP	(2 <i>R</i> 4 <i>R</i>) or (2 <i>S</i> , 4 <i>S</i>)bis(diphenylphosphino)pentane
Boc	Benzyloxycarbonyl
CuAAC	Copper(I)-catalyzed azide–alkyne cycloaddition
DBU	1,8-Diazabicycloundec-7-ene
DFT	Density Functional Theory
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dr	Diastereomer ratio
E	Ester group
<i>ee</i>	Enantiomer excess
FVP	Flash Vacuum Pyrolysis
h	Hour(s)
IR	Infra-Red
Me	Methyl
Ms	Mesyl
MW	Microwave
<i>n</i> -Bu	Normal butyl
Ni(cod) ₂	Bis(cyclooctadiene)nickel(0)
NMR	Nuclear Magnetic Resonance
P(<i>n</i> -Bu)Ad ₂	Di(1-adamantyl)- <i>n</i> -butylphosphine
Ph	Phenyl
Rh ₂ (esp) ₂	Bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)]
Rh ₂ (oct) ₄	Rhodium tetra octanoate
Rh ₂ (piv) ₄	Rhodium pivalate
Rh ₂ (<i>S</i> -DOSP) ₄	Tetrakis[(<i>S</i>)-(-)- <i>N</i> -(p-dodecylphenylsulfonyl)prolinato]dirhodium (II)
Rh ₂ (<i>S</i> -PTAD) ₄	Tetrakis[(<i>S</i>)-(+)-(1-adamantyl)-(N-phthalimido)acetato]dirhodium(II)
rt	Room temperature
TBDMSO	<i>tert</i> -Butyldimethylsilyloxy
Tf	Trifluoromethanesulfonyl (triflyl)
Tf ₂ O	Triflic anhydride
Tpm ^{*,Br}	Tris(3,5-dimethyl-4-bromopyrazolyl)methane]
Ts	Tosyl 4-toluenesulfonyl

1 Introduction

Rearrangements and transformations of heterocyclic rings constitute a special and interesting approach to other heterocyclic compounds [1–14]. These processes are often occurring via interesting but little known reaction mechanisms. The ring-chain tautomerism of 1,2,3-triazoles was discovered more than 50 years ago [7]. Following this, it has been shown that reversible ring opening of the 1,2,3-triazole ring followed by re-cyclization to form other rings are the key steps for the Dimroth, Conforth and L'abbé rearrangements [1–32].

Thermal transformation of 1,2,3-triazoles was also discovered and studied in the second part of the twentieth century. Owing mainly to work of MacNab, Wentrup, Rees, Gilchrist and L'abbé (Sect. 4) [33–44] it has been shown that 1,2,3-triazoles are good substrates for their thermal transformation to various heterocyclic compounds such as isoquinolines, indoles, pyrazines, and oxazoles. However, as the rule the yields of the products are rather moderate and in some cases even poor.

In the beginning of the twenty-first century 1,2,3-triazoles became very fashionable and rather available compounds due to the discovery of the CuAAC reaction by the Sharpless/Fokin and Meldal groups [45, 46]. Apart from the applications in medicine, biology, and analytical chemistry they were investigated as unique substrates for the generation of azavinyl carbenoid compounds that are rather reactive but stable enough to be involved in cycloadditions to double and triple bonds and for insertion to C–H, N–H, O–H and C–C bonds. Mainly by the efforts of Gevorgyan, Fokin and Murakami the new paradigm “transition-metal-catalyzed denitrogenative transformation of 1,2,3-triazoles” was developed since 2008 (Sect. 5) [47–79]. The denitrogenative approach has many advantages in comparison with traditional methods and constitutes an efficient, single step inter-conversion of 1,2,3-triazoles into a huge variety of other heterocyclic compounds and other valuable organic compounds such as cyclopropanes, cyclopropenes, enamines and diazadienes. Interestingly, 4-*N*-phthalimido-1,2,3-triazoles, as shown by the Davies group in 2012 [44], are suitable precursors of azavinyl carbenes on smooth heating even without catalyst.

Herein, we examine the rearrangements of 1,2,3-triazoles and their ring transformation into other heterocyclic compounds accompanied by elimination of dinitrogen, involving subsequent reactions with double and single bonds. Data on the ring-chain tautomerism of 1,2,3-triazoles are also included because of their importance for both the rearrangements and the dinitrogenative ring transformations of 1,2,3-triazoles. The latter part has been recently reviewed by Chattopadhyay and Gevorgyan [45]; however, even in the short time since then more articles on the transformations of 1,2,3-triazoles have been published than those included in the review [45].

2 Ring Chain Tautomerism (Diazoimine – 1,2,3-Triazole Equilibrium)

The ring-chain tautomerism is a phenomenon that is very important in 1,2,3-triazole chemistry, being an essential part of numerous rearrangements and ring transformations. The open chain isomers, diazoimines (chain isomer) **1** are, with a few exceptions, very unstable and undergo spontaneous ring closure to form 1,2,3-triazoles (ring isomer) **2** when they are generated [1] (Scheme 1).

As an example, the diazo group transfer reaction with benzenesulfonyl azide to amidine **3** furnishes a mixture of isomeric triazoles **4** and **5**, most probably via unstable intermediate diazoamidines **6** (Scheme 2). Many other examples are published confirming the higher stability of the triazole ring in comparison with the isomeric diazoimines [2].

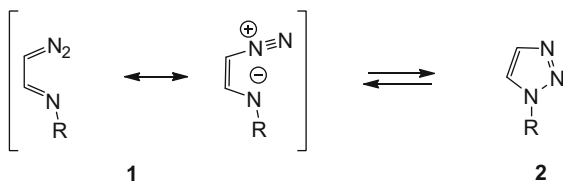
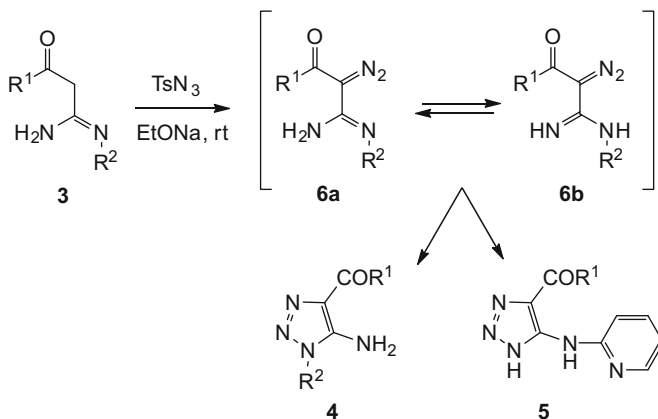
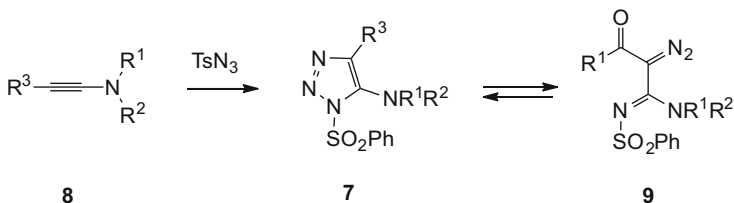
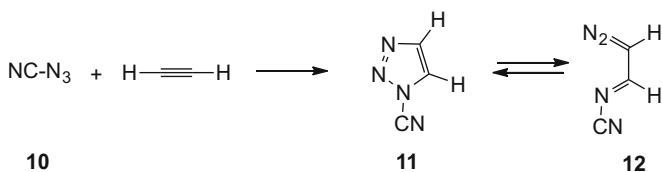
Interestingly, 1-sulfonyl-5-dialkylamino-1,2,3-triazoles **7** prepared by cycloaddition reaction of benzenesulfonyl azide to *N,N*-dialkylamino propynes **8** partially undergo ring opening reaction to give, according to IR and NMR spectroscopic data, an equilibrium mixture of triazoles **7** and diazo-amidines **9** [3] (Scheme 3). The existence of this type of equilibrium was the background for the discovery of rearrangements and metal catalyzed denitrogenative transformations of 1,2,3-triazoles (see Sects. 3 and 5).

Another well-known example of the synthesis of relatively stable diazoimines **12** is formed by the reaction of cyanogen azide **10** with acetylene to form a cycloadduct which, according to IR and NMR spectra, exists in solution as a ring-chain tautomeric mixture of 1-cyano-1,2,3-triazoles **11** and α -diazo-*N*-cyanoethylideneimine **12** (Scheme 4). An increase of the temperature and decrease of the polarity of the solvent were shown to shift the equilibrium in favor of the diazoimine form [4].

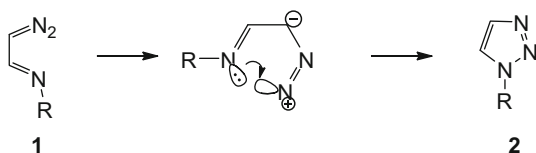
An ab initio and Density Functional Theory (DFT) study was carried out and 1H-1,2,3-triazole **2** was found to be 15–20 kcal/mol stable than diazoethaneimine **1** (Scheme 5). The very low activation energy (9–12 kcal) for the cyclization was explained in terms of a heteroelectrocyclic (pseudopericyclic [5]) mechanism where an input of energy to rotate the terminal groups was not required since the formation of the new N–N bond occurs by the in-plane interaction of the lone pair of electrons on the nitrogen atom of the imino group with the vacant orbital located at the terminal nitrogen atom of the diazo group [6].

The equilibrium between 2-diazomalondiamides **13** and 5-hydroxy-1,2,3-triazoles **14** in ethanol solution is shifted to the chain form [7] (Scheme 6).

Conversely, the equilibrium between α -diazo- α -cyanoacetamides **15** and its cyclic isomers **16** in the same conditions is shifted to the ring form [8]. The position of the equilibrium was shown to depend strongly on the nature of the solvent. It is shifted towards the cyclic form in polar solvents like water, acetonitrile, and DMSO. On the other hand, the diazo form is predominant in nonpolar benzene solution (see Table 1).

**Scheme 1** Diazoimine – 1,2,3-triazole equilibrium**Scheme 2** Reaction of acetamidines **3** with tosyl azide**Scheme 3** Reaction of ynamines with tosyl azide**Scheme 4** Cycloaddition of cyanogen to acetylene

Scheme 5 The heteroelectrocyclic (pseudopericyclic) mechanism for cyclization of diazoimine **1** to triazole **2**



Scheme 6 Tautomerism in the diazomaloamide **13** – 5-hydroxy-1,2,3-triazole **14** system

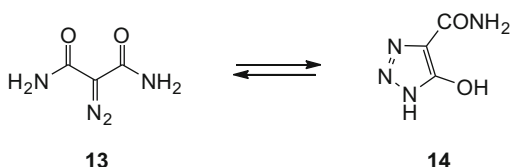
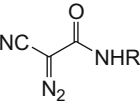
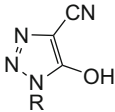
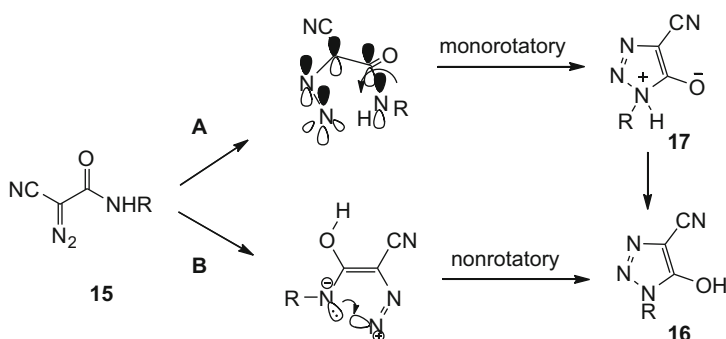


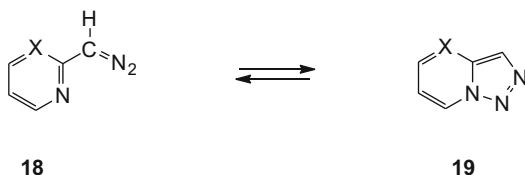
Table 1 The constants of equilibrium between diazo compounds **15** and triazoles **16**

						
15 a-c	16 a-c					
K = [16]/[15] at 35°C in various solvents						
R	D ₂ O	CD ₃ CN	DMSO-D ₆	Acetone-D ₆	C ₆ D ₆	C ₂ D ₅ OD
4-MeO-C ₆ H ₄	>100		21 ± 3	16 ± 1	0.7 ± 0.1	16 ± 2
Me	45.4 ± 2.1	27 ± 2	3.2 ± 0.8	1.2 ± 0.2	0.3 ± 0.02	11 ± 1
Bn	60 ± 9		6.2 ± 0.2	1.5 ± 0.2	0.24 ± 0.03	19.0 ± 0.8



Scheme 7 Cyclization mechanisms of 2-cyano-acetamides **15**

Based on quantum chemical calculations, kinetic studies, and differences in values of the kinetic isotope effect, a conclusion was made on a difference in mechanisms for the cyclization of *N*-alkyl- and *N*-aryldiazoacetamides **15** (Scheme 7). Cyclization of *N*-alkyl derivatives takes place via a monorotatory



X = CH ($\Delta\Delta G = -2-6$ kcal/mol) X = N ($\Delta\Delta G = -\{16-18\}$ kcal/mol)

$\Delta\Delta G = \Delta G_{18} - \Delta G_{19}$

Scheme 8 Relative stabilities of diazoimine and triazole forms in heterocyclic systems

mechanism, while cyclization of the *N*-aryl derivatives takes place by a mechanism where one of the steps is heteroelectrocyclization of 2-diazoacetimidates **17**. [8]. The same mechanisms for the cyclizations of *N*-alkyl- and *N*-arylmalonamides were confirmed by kinetic and theoretical studies of non-symmetrically substituted malondiamides [9].

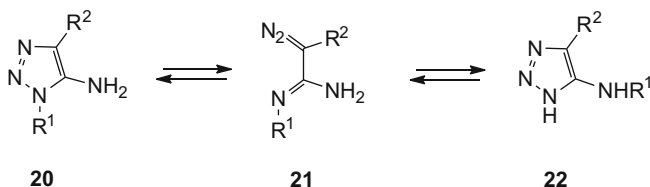
If the imino group is part of an aromatic heterocycle, then it has been shown by careful theoretical study that the relative stability of the diazoimine form increases in comparison with the ring form [10]. In the case of a pyridine ring, the cyclic form **19** is still (2–6 kcal/mol) more stable but the difference in free energies between the cyclic and ring forms is less than for the parent compounds **1** and **2** (15–20 kcal/mol) (Scheme 8). The relative free energy of diazo-pyrimidine **18** (X=N) is even 16–18 kcal/mol less in comparison with the cyclic form **19**. Depending on the nature of the heterocycle, either form can be more stable.

3 Rearrangements of 1,2,3-Triazoles

1,2,3-Triazoles are prone to undergo various ring transformations and rearrangements. This is the base for unique synthetic methods and makes room for the fundamental study of unusual reactions. Rearrangements of 1,2,3-triazoles are governed by the following factors: (1) the facile cleavage of the weak N1–N2 bond, (2) the existence of an equilibrium between 1,2,3-triazoles and α -diazoimines (see Sect. 2), and (3) the capacity of both imino- and diazo groups to cyclize onto electrophilic and nucleophilic functionalities. L'abbé proposed a classification for rearrangements of five-membered heterocyclic compounds depending on the number of participating side-chain atoms [11].

3.1 Dimroth Type Rearrangements

The term “Dimroth rearrangement” was introduced in 1963 [11] as a process of isomerization for 1-substituted 1,2,3-triazoles of type **20** to 5-amino substituted



Scheme 9 Dimroth rearrangement of 1,2,3-triazoles

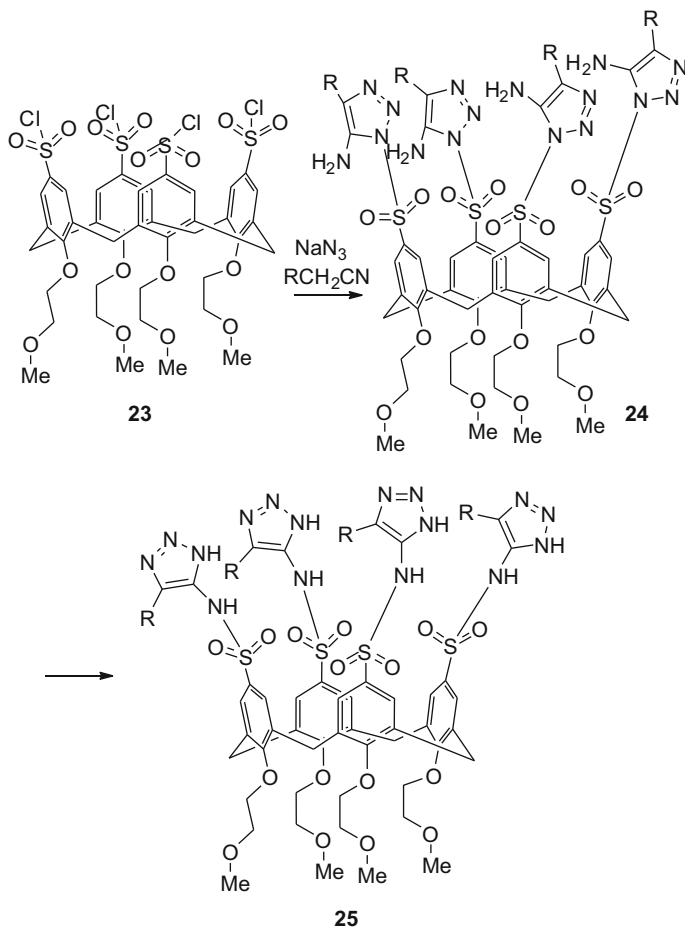
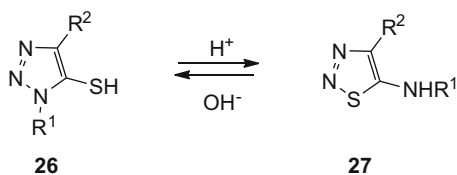
1,2,3-triazoles **22** taking place by ring opening to generate diazo acetamidines **21** and subsequent recyclization of the latter, after amidine tautomerization, onto the nitrogen atom of the former amino group attached to the ring to furnish the final product (Scheme 8). The cyclization of the diazo group onto the nitrogen atoms of a pivotal amidine fragment is a common feature of this type of rearrangement. This rearrangement was first described by O. Dimroth for the isomerization of 1-aryl-5-amino-1,2,3-triazole **20** to 5-anilino-1,2,3-triazoles **21** [7] and afterwards has received much attention in many publications including a couple of reviews [11–14].

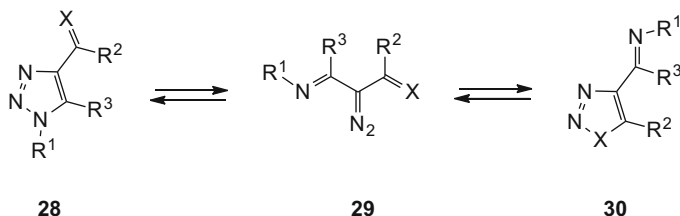
The position of the equilibrium depicted in Scheme 9 is shifted towards the acidic form **22** in basic solvents. The more basic the solvent the higher is the ratio **22/20** in the equilibrium mixture. Another tendency is that electron-withdrawing and bulky substituents stabilize the form where they are attached to the exocyclic nitrogen atom. On the other hand, alkyl groups, amino and aryl groups tend to favor the cyclic atom [11]. When R is an arylsulfonyl group, the rearrangement of **24** is so fast that only the rearrangement product, triazole **25** was isolated in the reaction of tetrakis-(azidosulfonyl)calix[4]arenes **23** with 2-cyanoacetamides [15] (Scheme 10).

5-Mercapto-1,2,3-triazoles **26** are capable of rearranging in acidic solution to isomeric 5-amino-1,2,3-thiadiazoles **27** (Scheme 11). However, the reverse reaction is more favorable in the presence of bases and in fact represents a general method for the synthesis of 5-mercapto-1,2,3-triazoles **26** [11, 15, 16].

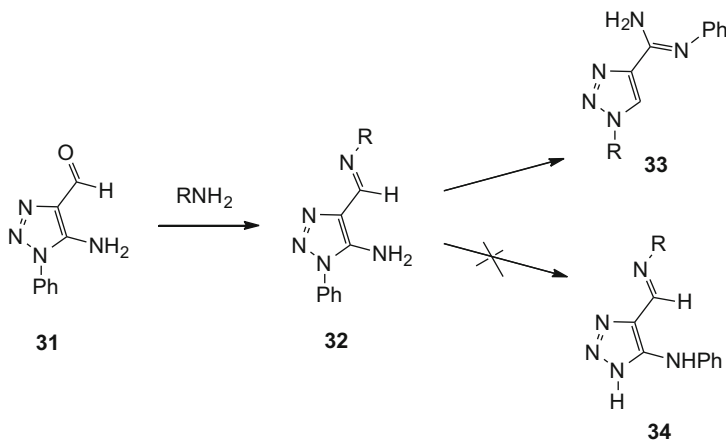
3.2 Cornforth-Type Rearrangements

Rearrangements of 1,2,3-triazoles of type **28** bearing a C=N, N=N, and C=S functions at the position 4, to isomeric triazoles **30** were mainly found, carefully studied, and reviewed in the L'abbé laboratory [17–20] (Scheme 12). These involve two atoms of the 4-substituents and are somewhat similar to the interconversion reactions of isomeric 4-acyl-substituted oxazoles via dicarbonyl nitrile ylides discovered by Cornforth in 1949 [1]. The competitive cyclizations of the intermediate diazo function of compound **29** onto the nitrogen atoms of both imino groups are a key feature of this type of rearrangement.

**Scheme 10** Dimroth rearrangement of tetrakis-(1,2,3-triazole-5-aminosulfonyl)-calix[4]arenes**Scheme 11** Rearrangement of 5-mercapto-1,2,3-triazoles **26** to 5-amino-1,2,3-thiadiazoles **27**



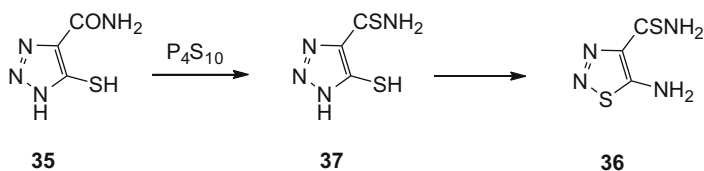
Scheme 12 Rearrangement with participation of two atoms of the side chain



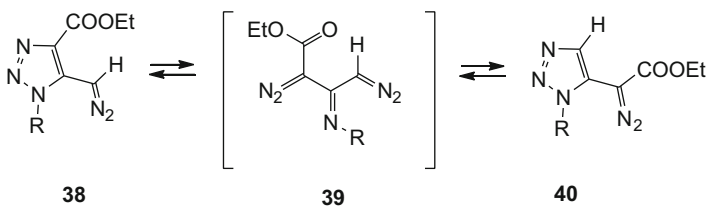
Scheme 13 Competition of Dimroth and Cornforth rearrangements

L'abbé and Vandendriessche made the design and synthesis of 1,2,3-triazoles **32** bearing amino and iminocarbonyl functions in positions 5 and 4 of the ring. Triazoles **32** are in principle capable of transferring via either Dimroth or Cornforth rearrangements to isomeric triazoles **33** or **34** [19]. It has been shown that triazoles **32** rearrange thermally to 4-amidino-substituted triazoles **33** instead of undergoing the Dimroth rearrangement to 5-anilino-triazoles **34** (Scheme 13). The rearrangement takes place for different R groups including alkyl, aryl, hydroxyl, and amino group, showing the generality of the process [18]. As in the case of Dimroth rearrangement, the equilibrium is shifted towards the triazole form possessing the strongest electron-withdrawing substituent at the imine nitrogen.

If C(X)R^2 in **28** is substituted by an azo group, a rearrangement can occur to form a tetrazole ring. Thus an attempted crystallization of 5-hydroxy-4-phenylazo-1,2,3-triazole in acetic acid led to its complete isomerization to 2-phenyl-tetrazole 4-carboxamide [21]. When 5-mercapto-1,2,3-triazole-4-carboxamide **35** was reacted with P_4S_{10} in dioxane the formation of 5-amino-4-carbothioamide **37** occurred most probably via Cornforth-type rearrangement of intermediate 5-mercapto-1,2,3-triazole-4-carbothioamide **36** (Scheme 14) [22].



Scheme 14 Cornforth type of rearrangement of 1,2,3-triazole **37** to 1,2,3-thiadiazole **36**



Scheme 15 L'abbé rearrangement of 5-diazomethyl-1,2,3-triazoles

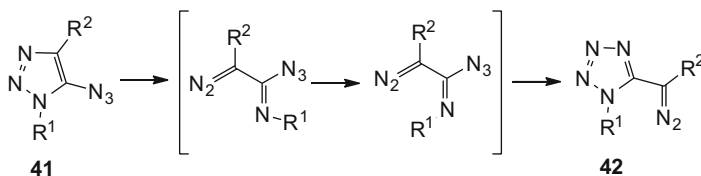
Cornforth type rearrangements are also known for fused 1,2,3-triazoles, for instance:

- 4-amino-1-(arylsulfonyl)benzo[*d*]1,2,3-triazoles to 4-(arylsulfonyl aminobenzo[*d*]1,2,3-triazoles [23]
- 3H-[1,2,3]triazolo[4,5-*b*]pyridine-7-amine to 1H-[1,2,3]triazolo[4,5-*c*]pyridine-4-amine [24]
- 3H-[1,2,3]triazolo[4,5-*b*]pyridine-7-(4H)thione to [1,2,3]thiadiazolo[4,5-*c*]pyridine-4-amine [24]

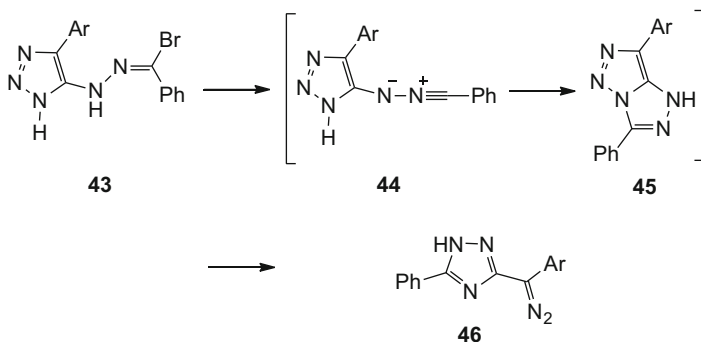
3.3 *L'abbé Type Rearrangements*

Competitive 1,5-cyclizations of a single imino group onto two 1,3-dipole moieties are another type of rearrangements for 1,2,3-triazoles. An example for this kind of reaction, found by L'abbé and Dehaen, was the rearrangements of 5-diazomethyl-4-ethoxycarbonyl-1,2,3-triazoles **38** to diazoacetates **40** (Scheme 15). The reaction is limited to triazoles bearing electron-withdrawing substituents at positions 1 and 4 of the ring [25, 26].

5-Azido-1,2,3-triazoles **41** bearing strong electron-withdrawing substituents at position 4 such as ester, cyano, aldehyde groups were found to undergo very similar rearrangement to form 5-diazomethyl-tetrazoles **42** [27–31] (Scheme 16). The introduction of an electron-withdrawing substituent at the position 1 of the ring increases the rate of the process. The rearrangement is faster in non-polar solvents, but the effect is small. The rate-limiting step of the reaction was shown to be the ring opening of the 1,2,3-triazole ring [27].



Scheme 16 L'abbé rearrangement of 5-azido-1,2,3-triazoles to 5-diazomethyl-tetrazoles

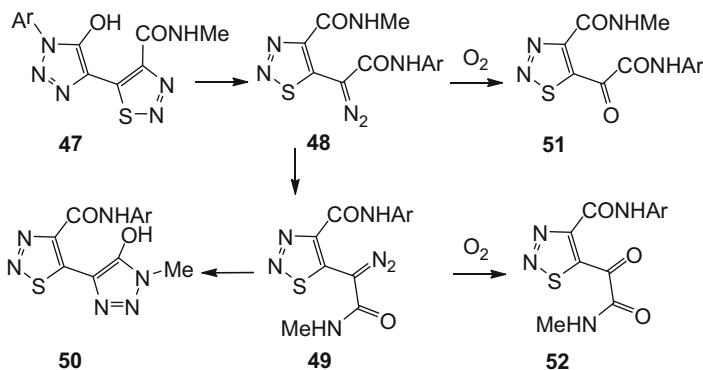


Scheme 17 L'abbé type of rearrangement of 1,2,3-triazol-5-yl nitrilimines to diazomethyl-1,2,4-triazoles

N-Unsubstituted 4-aryl-1,2,3-triazoles **43** bearing a hydrazonoyl bromide group at position 4 in water/acetone 1:1 solution undergo rearrangement to aryl (diazomethyl)-1,2,4-triazole **46** under elimination of HBr. One of the proposed mechanism includes the formation of intermediate nitrilimine **44** with subsequent 1,5-electrocyclic ring closure and ring opening to form final product **46** (Scheme 17).

3.4 Tandem Rearrangements

A single example of the rearrangement for heterocyclic ring conjugates, containing both a 1,2,3-triazole and 1,2,3-thiadiazole ring, was found as a collaboration of our laboratories. We have found that bis heterocycles **47** are capable of undergoing domino-type rearrangements involving both rings to form isomeric 5-(1,2,3-triazol-4-yl)-[1,2,3]-thiadiazoles **50** (Scheme 18). The net result of the process is the interchange of the aryl and methyl groups. The rearrangement proceeds as a three-step process and involves, first, ring opening of the hydroxytriazoles **47** to form diazoamides **48**. The latter undergo the L'abbé rearrangement to form isomeric diazo compounds **49**. Finally, a ring closure occurs to afford hydroxyl triazoles **50**. The formation of the intermediate diazo compounds **48** and **49** was



Scheme 18 Tandem rearrangement of thiadiazolyl triazoles **47** to thiadiazolyl triazoles **50**

confirmed by IR, ^1H and ^{13}C NMR spectroscopy of the products in the reaction mixture and of the chemical transformation of intermediate diazo compounds to ketones **51** and **52** [17].

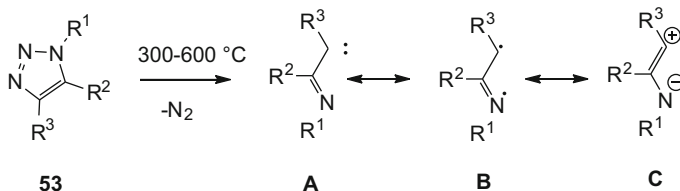
4 Thermolysis of 1,2,3-Triazoles

1,2,3-Triazoles are in general stable compounds due to their aromaticity. Therefore, normally a high temperature is required for the elimination of dinitrogen. To explain the variety of the products formed in the reactions, the generated species are represented as a carbene **A**, diradical **B**, or zwitterion **C** resonance form (Scheme 19).

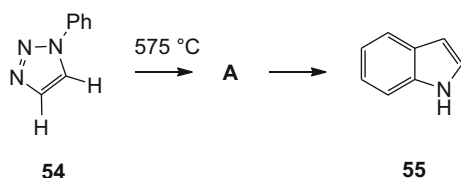
The presence of aromatic substituents stabilizing these forms **A–C**, or the introduction of strongly electron withdrawing substituents lowering the activation energy for the elimination of dinitrogen, are required to isolate the reaction products. If the substituents at N1 of the triazole ring or more commonly of benzotriazoles are capable of reacting intramolecularly with radicals, then cyclization occurs leading to a variety of different compounds including heterocyclic systems.

The formation of indoles **55** by thermolysis of 1-aryl-1,2,3-triazoles **54** was interpreted as a process proceeding from singlet form **A** followed by Wolff rearrangement and ring closure to final products [33, 34] (Scheme 20).

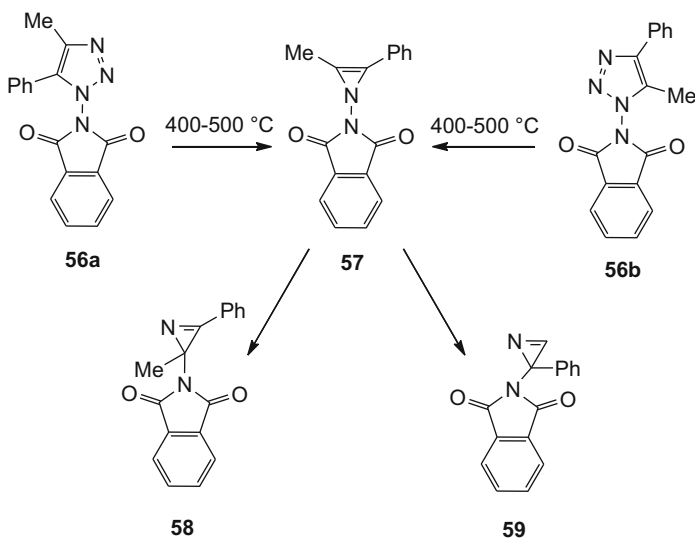
Vacuum pyrolysis of isomeric 1-*N*-phthalimido-1,2,3-triazoles **56a** and **56b** at 400–500°C was shown to yield the compounds **58–59** and the products of further transformation of the latter in the same ratio. Based on these results Gilchrist et al. [35, 36] postulated the formation of an identical intermediate 1H-azirine **57** for the reactions of both triazoles. The 1H-azirine **57** underwent isomerization to more stable isomeric 2H-azirines **58–59** (Scheme 21).



Scheme 19 Presentation of resonance forms A, B, C of the species formed in pyrolysis of 1,2,3-triazoles **53** at 300–600°C

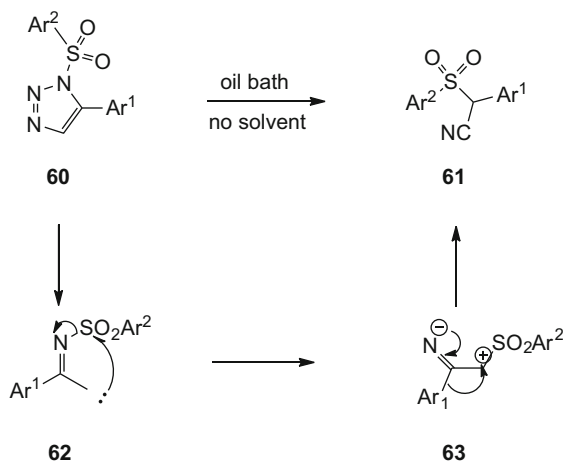
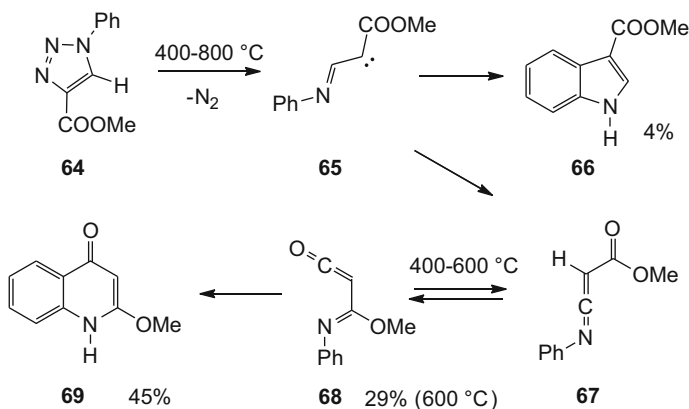


Scheme 20 Transformation of 1-phenyl-1,2,3-triazole to indole



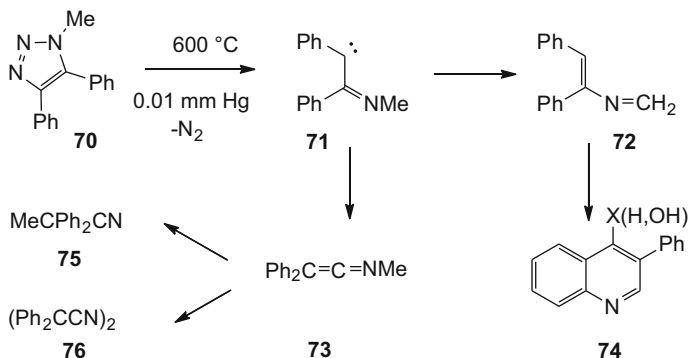
Scheme 21 Vacuum pyrolysis of trisubstituted triazoles

1-Sulfonyl-5-aryl-1,2,3-triazoles **60** were shown recently by the Croatt group to undergo very smooth and fast dinitrogen elimination at 140–190°C to afford α -sulfonyl nitriles **61** in 2–57% yield (Scheme 22). In the same study it was shown that if the temperature is not high enough for fast dinitrogen elimination, then isomerization of 1,5-disubstituted-1,2,3-triazole **60** to the 1,4-isomer took place. The proposed mechanism includes the formation of carbene species **62** in

**Scheme 22** Synthesis and mechanism for formation of sulfonyl nitriles**Scheme 23** Flash vacuum pyrolysis of methyl 1-phenyl-1,2,3-triazole-4-carboxylate

the first step. The second step involves a 1,3-sulfonyl shift either directly to zwitterion **63** or via a cyclic four-membered ring. Zwitterion **63** in turn underwent an aryl shift to form final product **61** [37].

Wentrup and Fulloon have carefully studied the transformation of methyl 1-phenyl-1,2,3-triazole-4-carboxylate **64** with preparative FVP and managed to isolate indole **66**, keteneimine **67**, and quinolone **69** [38]. They have also shown that elimination of dinitrogen from **64** occurs at 380°C and both keteneimine **67** and ketene **68** are observable by IR spectroscopy. Based on these experiments Wentrup and Fulloon proposed a mechanism (Scheme 23) explaining the skeletal rearrangement by interconversion of imidoylketene **67** to oxoketeneimine **68**, observed also by McNab et al. for ethyl 1-phenyl-1,2,3-triazole-4-carboxylate



Scheme 24 Flash vacuum pyrolysis of *N*-alkyl-4,5-diphenyl-1,2,3-triazoles

[39]. In the case of *N,N*-dimethyl-1-aryl-1,2,3-triazole-4-carboxamide, 2-*N,N*-dimethylquinolone was obtained [40].

The dinitrogen evolution in *N*-methyl-1,2,3-triazoles **70** required a very high temperature and was accompanied by formation of nitriles **75** and **76** via Wolff rearrangement together with formation of isoquinolines **74** [33]. It seems that the formation of compound **74** involves electrocyclization of **72** followed by oxidation to final product (Scheme 24).

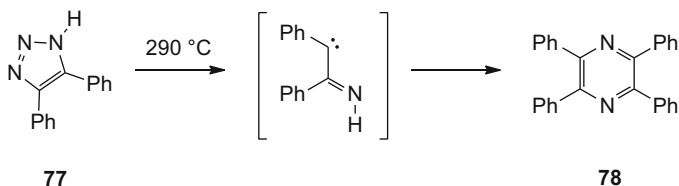
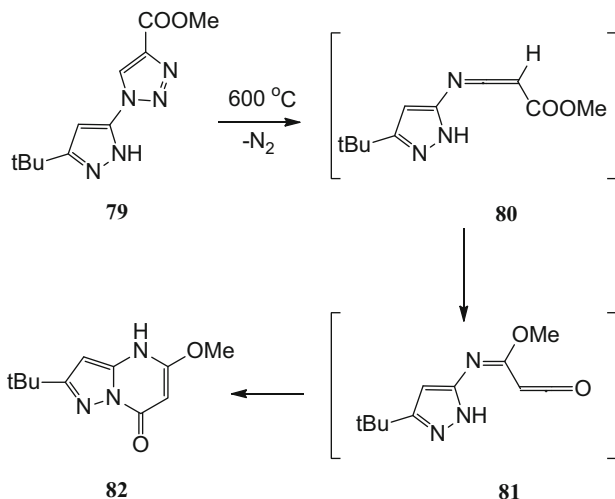
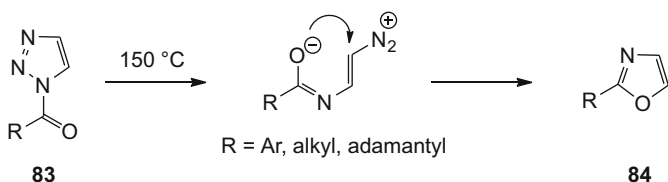
Interestingly, the formation of 2,3,5,6-tetraphenyl pyrazine **78** from 1-NH-triazole **77** occurred at lower temperature [13] (Scheme 25).

McNab et al. have shown that 1,2,3-triazole **79**, bearing both an ester group at position 3 and a pyrazol-3-yl moiety at N_1 is capable of transferring to pyrazolo-pyrimidine **82** after FVP at 600°C (10^{-2} to 10^{-3} Torr) [39]. From ^{13}C labeling experiments they concluded that the mechanism of the reaction involved a ketenimine–imidoylketene rearrangement (Scheme 26).

Transformation of a 1,2,3-triazole to an oxazole ring took place when 1-acyl-1,2,3-triazoles **83** were subjected to thermolysis at 150°C in sulfolane solution (Scheme 27). 2-Aryl- and 2-alkyloxazoles **84** were prepared in very good yields, allowing to recommend this transformation of 1-acyl-1,2,3-triazoles as a method of choice for the synthesis of 2-substituted oxazoles of type **84** [13].

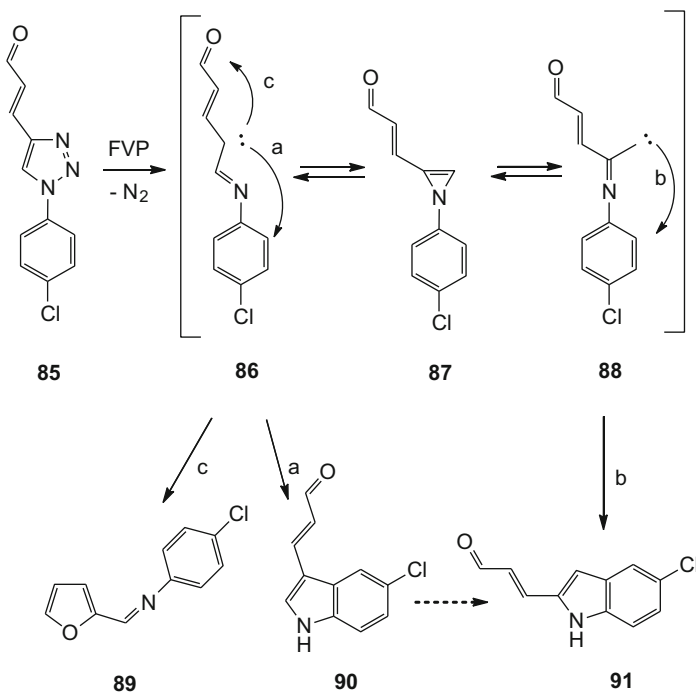
2-Substituted benzoxazoles can be prepared similarly to **84** by transformation of 1-acyl-benzo-1,2,3-triazoles. Because thermolytic reactions of benzotriazoles were reviewed a couple years ago [41] they are not included here.

The formation of furans **89** (48%) as main products together with a mixture of isomeric indoles **90** and **91** (46%) occurred when 4-acroleinyl-1-aryl-1,2,3-triazoles **85** were subjected to FVP at 400°C (Scheme 28). Because of the preponderance of 3-substituted indole **90** in the mixture of 2- and 3-acroleinylindoles the authors [42] made the conclusion that iminocarbene **86** formed first and insertion of this carbene into the aromatic C–H bond yielded directly indole **90**. The formation of indole **91** could take place either via rearrangement of carbene **86** to **87** via antiaromatic azirine **87** (pathway **b**) or by rearrangement from indole **90**. The

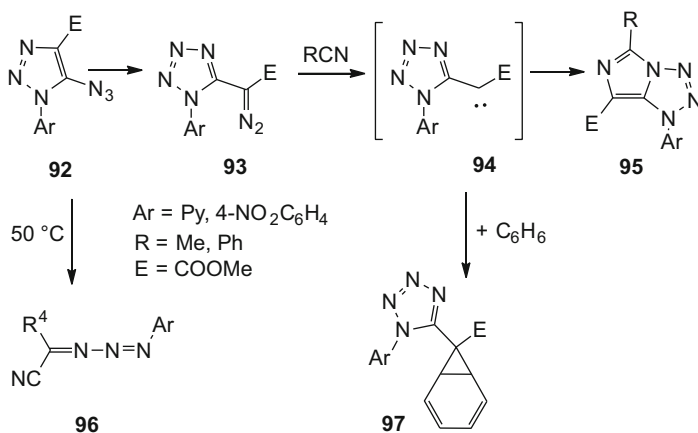
**Scheme 25** Thermolysis of 4,5-diphenyl-1,2,3-triazoles**Scheme 26** Flash vacuum pyrolysis of pyrazolyl-1,2,3-triazoles **79****Scheme 27** Thermolysis of 1-acyl-1,2,3-triazoles

presence of oxazole **89** in the reaction mixture was explained by 1,5-heteroelectrocyclization in which the carbene carbon atom attacks the oxygen atom lone pair of electrons to form a furan ring.

Heating of a solution of **92** in either acetonitrile or benzonitrile leads to evolution of dinitrogen to form 5-methylimidazo tetrazole **95** (R=Me) or 6-phenyl imidazo-tetrazoles **95** (R=Ph) in 65 and 59% yield, respectively (Scheme 29). The mechanism of this transformation included the rearrangement of 5-azidotriazoles to 5-(α -methoxycarbonyl)diazomethyl tetrazoles followed by elimination of dinitrogen

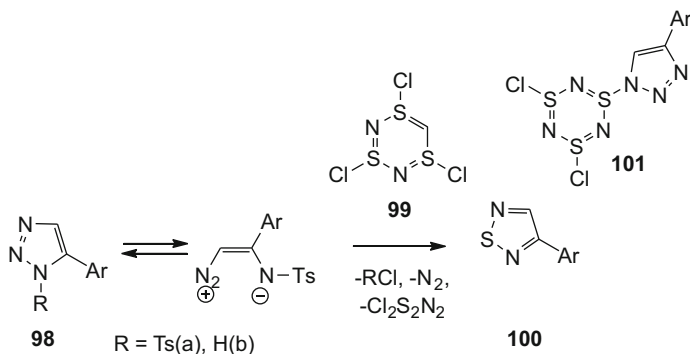


Scheme 28 Flash vacuum pyrolysis of 4-acroleinyl-1-aryl-1,2,3-triazoles **85**



Scheme 29 Thermolysis of 5-azido-1,2,3-triazoles **92**

to form intermediate carbenes **94**. The latter were subjected to cycloaddition reaction with nitriles to form final products **95**. Intermediate diazo compounds **93** were identified by IR and NMR spectroscopy and intermediate carbenes were trapped by



Scheme 30 Conversion of 1,2,3-triazoles **98** to 1,2,5-thiadiazoles **100**

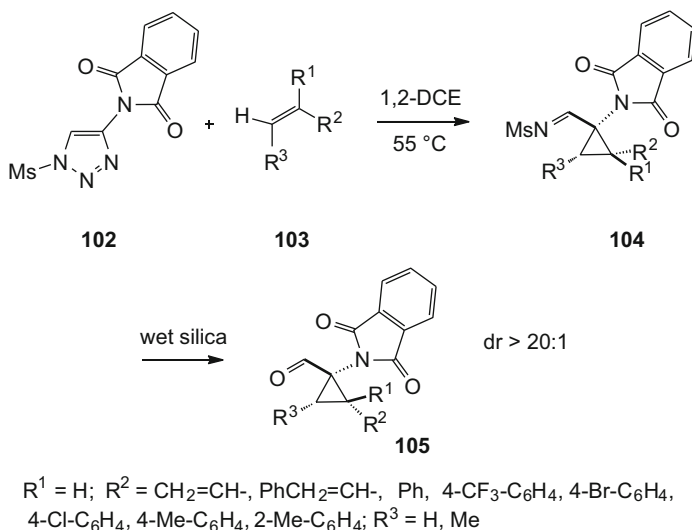
benzene to form norcaradienes **97**. Interestingly, heating of 5-azido-1,2,3-triazoles **92** in petroleum ether at 50°C afforded benzyldiene triazenes **96** [27].

Rees and Yue have discovered that a 1,2,3-triazole ring **98**, bearing electron-withdrawing substituents, can be transferred by treatment with trithiazyl trichloride **99** in boiling tetrachloromethane to 1,2,5-thiadiazole **100** [43] (Scheme 30).

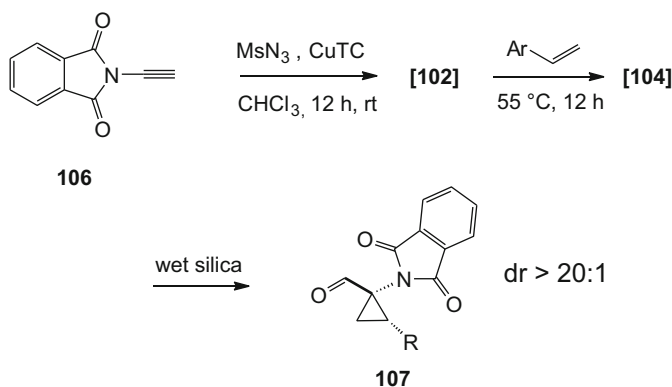
Interestingly, the presence of an *N*-tosyl group is not crucial to the reaction although the yield is higher (90%) in the reaction of 1-tosyl-5-nitrophenyl-1,2,3-triazole **98a** in comparison with the reaction of 5-nitrophenyl-1,2,3-triazole **98b** (67%). Because 4-phenyl-1,2,3-triazole did not give 3-phenyl-1,2,5-thiadiazole on treatment with trimer **99** under the same conditions the authors made the conclusion that the presence of a *p*-nitro group is crucial to the reaction. This could indicate that trithiazyl trichloride **99** does not react with the intact triazole but requires at least a small amount of diazoimine tautomer. Rees and Yue proposed that the reaction could go via intermediate **101** in which the triazole is activated to ring opening just as it is in the *N*-tosyl derivative.

Cyclopropanes bearing both carboxaldehyde and disubstituted amino groups of type **105** were successfully synthesized by cyclopropanation of donor/acceptor carbenes in which the donor group is a protected amine functionality [44] (Scheme 31).

Alford and Davies demonstrated that 4-*N*-phthalimido-*N*-sulfonyl-1,2,3-triazoles **102** are suitable precursor of such kind of carbenes [44]. Thus triazole **102** is shown to react smoothly at 55°C with styrene without catalyst to form cyclopropane imine **104** (Scheme 31). The latter is susceptible to hydrolysis and was easily transformed to aldehyde by treatment with wet silica in excellent yield and high diastereoselectivity. The scope of the reaction with respect to the alkene was examined. A broad range of terminal and internal alkenes, or styrenes bearing either electron-rich or electron-deficient aryl groups, reacted smoothly in good to excellent yields with high diastereoselectivity. Dienes are also capable of reacting with one of the two double bonds with triazole **104** to form cyclopropane alkenes.



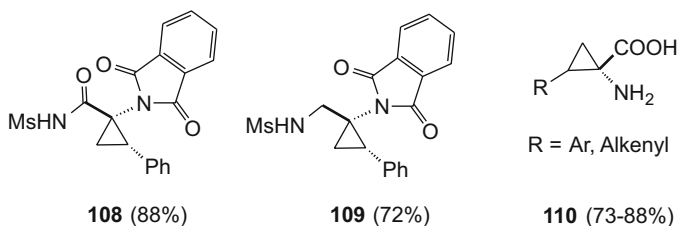
Scheme 31 Syntheses of cyclopropanes **104**, **105**



Scheme 32 Synthesis of cyclopropane **107**

The synthesis of α -amino cyclopropane aldehydes is shown to be conducted in a one-pot protocol starting from *N*-ethynylphthalimide **106**. The latter being treated with mesyl azide in the presence of CuCN in chloroform generates 4-phthalimido-*N*-mesyl-1,2,3-triazole **102** [44].

Reaction of intermediate product **102** with styrene at 55 °C proceeds within 12 h (Scheme 32). The subsequent treatment of the reaction mixture with wet silica finalizes the process to furnish aldehydes **107** in good yields (74–85%) and with high diastereoselectivity (>20:1). The initial products of the thermal cyclopropanation, sulfonyl imines of type **104** are shown to be valuable reagents in the synthesis of α -amino cyclopropane derivatives [44] (Scheme 33).

**Scheme 33** Structures of cyclopropanes **108–110**

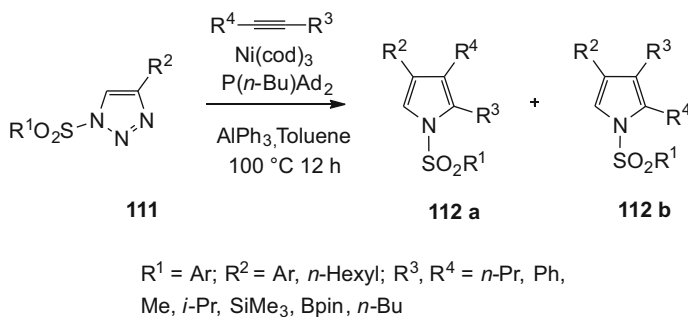
Thus, reduction of **104** with sodium borohydride provided an access to amino substituted cyclopropane **109**. On the other hand, the oxidation of **104** with sodium chlorite according to a Pinnick reaction affords sulfonyl amides **108**. It is worth noting that α -amino cyclopropane aldehydes can be easily converted to cyclopropane α -amino acids **110** by mild Pinnick oxidation of the aldehyde group to the acid, followed by the deprotection of the *N*-phthaloyl moiety by either direct hydrolysis or sodium borohydride reduction [44].

5 Metal Catalyzed Transformations of 1,2,3-Triazoles

Though ring transformations and rearrangements of 1,2,3-triazoles are known from the mid of last century, the use of metal catalysis is a recent trend in the development of 1,2,3-triazole chemistry. Starting from 2007 with reports from the Gevorgyan group and just afterwards by Fokin and Murakami, this new chemistry underwent a very fast evolution comparable to the exponential growth of the chemistry of 1,2,3-triazoles after introduction of the click-reaction concept by Sharpless in 2001. The short review and highlights were published in 2012 and 2013, respectively [47, 48]. Because many publications appeared in 2012 and especially in 2013, that were not included there, these do not cover all aspects of metal catalyzed denitrogenative transformation of 1,2,3-triazoles. This section includes a review of metal catalyzed transformation of 1,2,3-triazoles with focus on the new reports that were not covered in the previous reviews [47, 48]. The data are classified on the reaction type products.

5.1 Synthesis of Pyrroles

Pyrroles are known structural motifs in pharmaceutical agents including a number of natural products. Thus the development of new, efficient methods for their synthesis from readily accessible compounds remains an active field. The protocol of denitrogenative transannulation was recently used for the synthesis of monocyclic, functionalized, and fused pyrroles from easily available



Scheme 34 Reaction of *N*-sulfonyl 1,2,3-triazoles **111** with alkynes

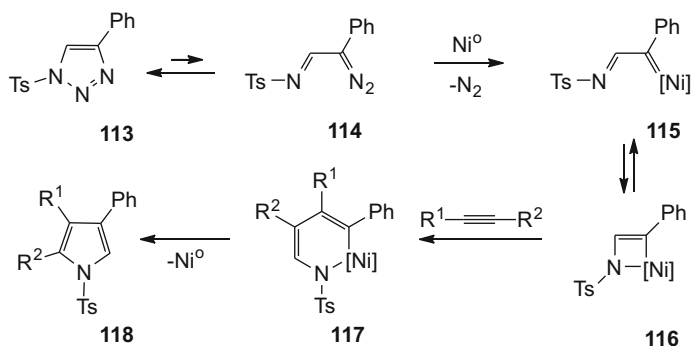
1-sulfonyl-1,2,3-triazoles, 1-(1,2,4-triazol-5-yl)-1,2,3-triazoles, and [1,2,3]-triazolo[1,5-*a*]pyridines [47–59].

The syntheses of monocyclic tetra-substituted and 1,2,4-trisubstituted-*N*-tosyl pyrroles by denitrogenative reaction of *N*-tosyl-1,2,3-triazoles **111** with nickel and rhodium catalysts were reported by the Murakami [49] and Gevorgyan [52] groups, respectively (Scheme 34). Murakami and co-workers have discovered that the reaction of *N*-sulfonyl-1,2,3-triazoles with [Ni(cod)₂] catalyst in the presence of bulky phosphine ligands and AlPh₃ is efficient for the transformation of 4-aryl-1,2,3-triazoles to tetra-substituted pyrroles after treatment with internal alkynes [49]. Symmetrical alkynes reacted with *N*-sulfonyl triazoles **111** to afford pyrroles **112** in good yields, except for the 3-*n*-hexyl derivative. Interestingly, the reaction with nonsymmetrically substituted 1,2-dialkynes generates nearly equal amounts of isomeric pyrroles **112a** and **112b**. Terminal alkynes were found not to enter to the reaction probably due to the facile self-oligomerization side reaction.

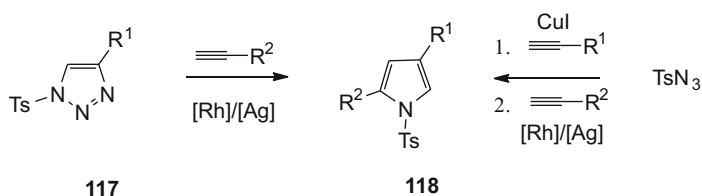
The mechanism of the reaction proposed by Murakami and co-workers [49] is outlined in Scheme 35. According to this report, the process starts from the ring opening of triazole ring **113** to form the isomeric diazo-imine form **114**. An equilibrium exists between ring and chain isomers which is shifted far in favor of the cyclic form. Nickel adds onto the diazo function which releases nitrogen to form a nickel carbenoid **115** that can be in an equilibrium in cyclic form **116**. The insertion of an alkyne into the Ni–C bond of the latter leads to a six-membered nickelacycle **117**. Reductive elimination of Ni⁰ furnishes the final product **118**.

Gevorgyan et al. have discovered that involvement of terminal alkynes required the use of a Rh₂(oct)₄/AgOCOCF₃ binary system containing both a rhodium catalyst and a Lewis acid, and the usage of nonpolar solvents such as toluene or hexane, under 70 °C [50] (Scheme 36).

These conditions have shown to be efficient for ring transformation reactions of a wide range of *N*-tosyl-1,2,3-triazoles with various electron-rich aryl alkenes (Scheme 36). The authors managed to combine the synthesis of triazole **117** from alkyne and copper iodide and denitrogenative reaction of *N*-tosyl-1,2,3-triazole **117** to a three component semi-one-pot protocol for pyrrole **118**.

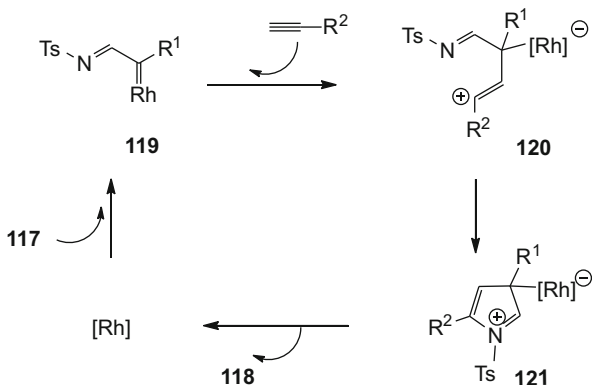


Scheme 35 Proposed mechanism of the nickel-catalyzed denitrogenative transannulation of triazole **113** with internal alkynes



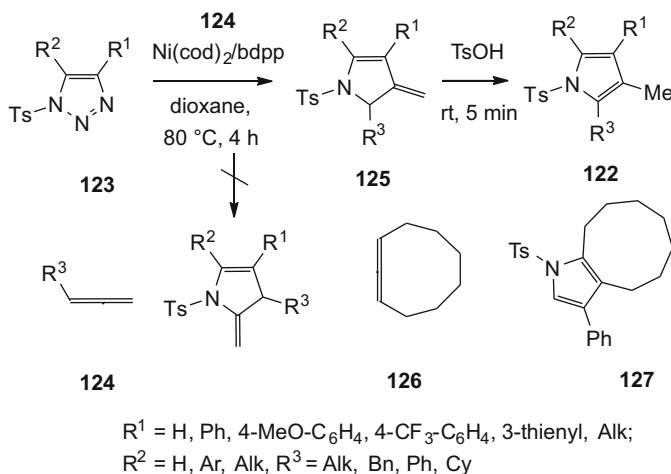
R¹ = Ar, Alk, CO₂Et, H; R² = electron rich Ar and cyclohexen-1-yl

Scheme 36 Reactions of tosyl azide and *N*-sulfonyl-1,2,3-triazoles with terminal alkynes



Scheme 37 Proposed mechanism of transformation **117** to **118**

Three pathways were proposed [50] to explain the results of the denitrogenative transformation of triazole **117** to pyrrole **118** (Scheme 37). Based on an experiment with deuterated *o*-tolyl acetylene the authors [50] concluded that the most plausible

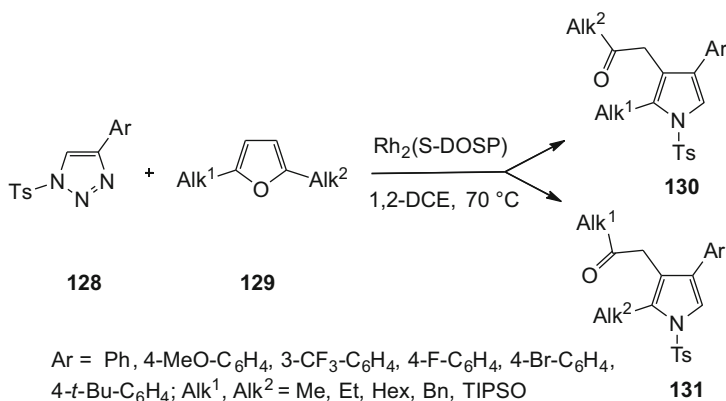


Scheme 38 Synthesis of poly-substituted pyrroles

mechanism includes the primary formation of Rh-iminocarbene **119** upon treatment of triazole **117** with $\text{Rh}_2(\text{oct})_4$ followed by direct nucleophilic attack of the terminal alkyne to the latter to produce ylide **120**. In its turn the ylide **120** forms upon cyclization the zwitterionic species **121**. Elimination of rhodium catalyst from the latter affords the final product **118** (Scheme 37).

Murakami and co-workers have been found that monocyclic polysubstituted pyrroles **122** can be efficiently prepared by regiocontrolled reaction of 1-sulfonyl-1,2,3-triazoles **123** and allenes **124** [51] (Scheme 38).

The same authors have also shown that the reaction takes place via initially formed isopyrroles **125**. The latter generally are less stable and rearrange to pyrroles **122**. Normally a mixture of isomeric pyrroles **122** and **125** is formed in this reaction. Interestingly, the reaction of 5-phenyl-1-tosyl-1,2,3-triazole **123** ($R^1 = \text{Ph}$, $R^2 = \text{H}$) with cyclonona-1,2-diene **126** produces only pyrrole **127**. The addition of *p*-toluenesulfonic acid is shown to be an efficient tool to accelerate the double bond isomerization [49]. This operation together with a nickel(0) catalyst was included to form a general protocol to prepare polysubstituted pyrroles by reaction of *N*-sulfonyl-1,2,3-triazoles **123** with allenes **124**. The authors have examined the generality of this reaction and have shown that various 5- and 4-substituted 1,2,3-triazoles **123** react well with undeca-1,2-diene to form the corresponding pyrroles **122** bearing both electron-withdrawing and -donating substituents at position 4 and 5 of the ring, respectively. Furthermore, 1,4,5-trisubstituted -1,2,3-triazoles **123** are shown to react with undeca-1,2-diene **124** to furnish tetrasubstituted pyrroles **122**. They have also shown that monosubstituted allenes give corresponding pyrroles in good yields. Apart from 1,3-disubstituted cyclic allene **126** that furnishes fused pyrrole **127**, other 1,3-disubstituted allenes are found to be unreactive.



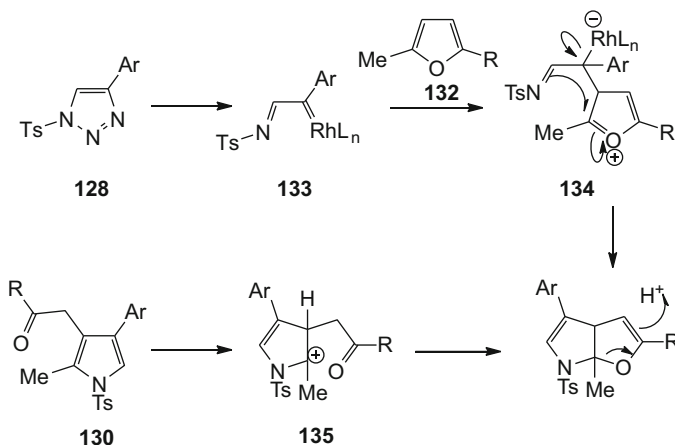
Scheme 39 Reaction of *N*-tosyl-1,2,3-triazoles with furans

An interesting example for the reaction of 1-tosyltriazoles **128** with the double bond of a α -excessive furan ring, leading to formation of pyrroles, was found by Davies with co-workers [52] (Scheme 39). In fact, the discovered reaction represents a novel convergent transformation. It has been shown that various 4-aryl-*N*-tosyl-triazoles **128** readily react with 2,5-dimethylfurans **129** in the presence of a rhodium catalyst to give pyrroles **130** in good yields. 2,5-Dialkylsubstituted furans **129** are shown to be excellent substrates for the pyrrole synthesis [52]. However, in many instances for asymmetrically 2,5-disubstituted furans mixtures of regioisomers **130** and **131** are formed, lowering the synthetic potential of the discovered reaction.

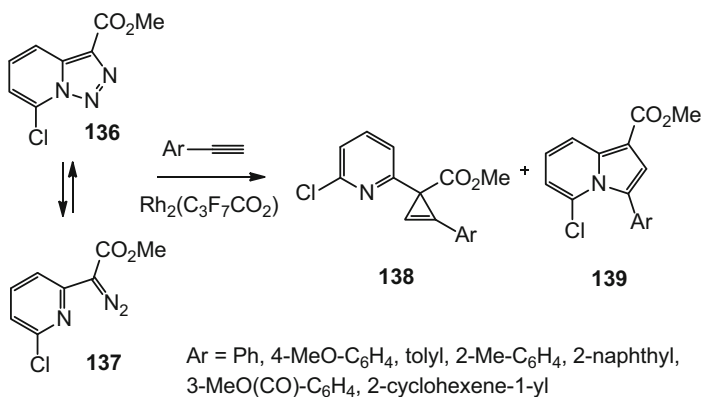
A plausible mechanism for the formation of pyrroles **130** is provided in Scheme 40.

The rhodium carbene complex **133**, formed from triazoles **128** after treatment with rhodium catalyst, attacks the C-3 carbon of furan to generate a cationic intermediate **134**. The latter undergoes cyclization, alternative ring opening, and aromatization of **135** due to deprotonation to afford final product **130**.

Based on the data for the equilibrium in solution between 7-chloro-pyrido [1,2-*c*]-1,2,3-triazoles **136** and 2-pyridyl diazoalkanes **137** and for experiments with triethylsilane, Gevorgyan and co-workers indicated that 7-halo-substituted pyridotriazoles **136** can serve as convenient precursors of Rh carbenoids [51] (Scheme 41). The reaction of 7-chloro-1,2,3-triazolo[1,5-*a*]pyridines **136** with arylacetylenes is shown to afford a mixture of 3-pyridyl cyclopropene **138** and indolizine **139**. The ratio of products formed is strongly dependent on the kind of rhodium catalyst. The use of rhodium acetate gives 68% of cyclopropene **138** and 28% of indolizine **139**. Remarkably, the use of rhodium(II) heptafluorobutyrate in the reaction of pyridotriazole **136** with a series of aryl and alkenyl alkynes proceeds chemoselectively to produce cyclopropenes **138** in good yields. Cyclopropenes **138** are still accompanied by 5–10% of indolizines **139**, which are easily separable by column chromatography [53].



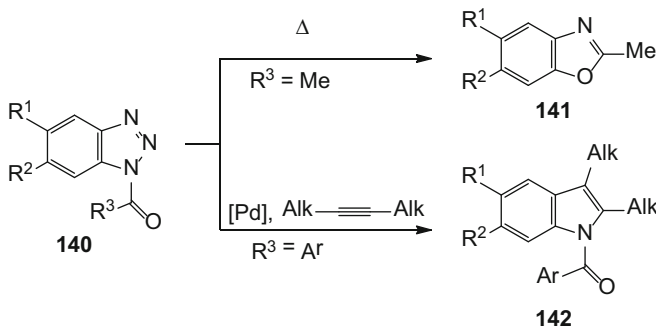
Scheme 40 Plausible mechanism for pyrrole formation from reaction of *N*-tosyltriazoles **128** with furans



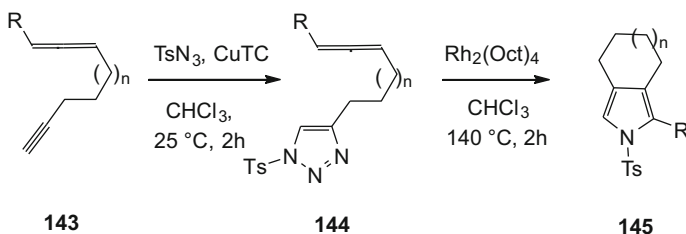
Scheme 41 Reaction of pyridotriazoles with terminal alkynes

In contrast to the thermal reaction of 1-acyl-1,2,3-triazoles ($\text{R}^3=\text{Me}$) where the formation of an oxazole ring takes place [41] to furnish compound **141**, the indolization of *N*-aroylbenzotriazoles occurs in the presence of palladium catalyst to form *N*-acylindoles **142** [54] (Scheme 42).

Denitrogenative reaction of *N*-tosyl-1,2,3-triazoles of type **144**, that were prepared by the copper(I) thiophene-2-carboxylate catalyzed Huisgen cycloaddition of acetylene **143** with TsN_3 , was applied by Schultz and Sarprong [55] for the synthesis of a series of 3,4-fused pyrroles **145** (Scheme 43). Pyrroles related to **145** have found practical application in the synthesis of dipyrromethene ligands and of the related natural product cycloprodigiosin [55]. Reaction of *N*-tosyl triazole **144** bearing the allene moiety as part of the molecule with $\text{Rh}_2(\text{oct})_4$ in chloroform at



Scheme 42 Transformation of *N*-acylbenzo[*d*]triazoles to indoles



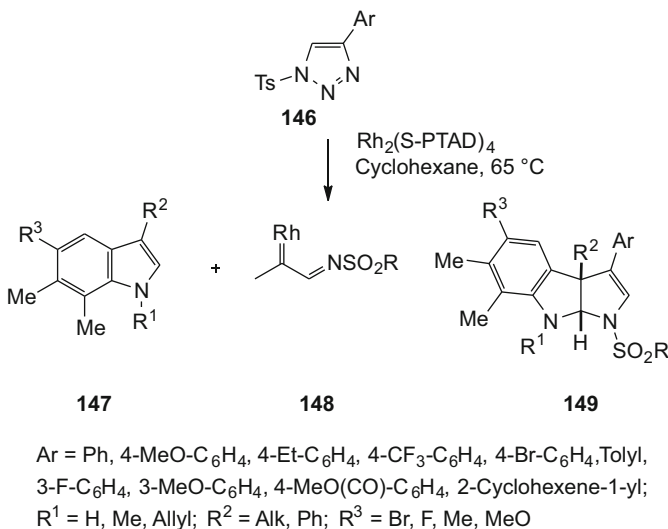
Scheme 43 Synthesis of fused pyrroles **145**

140°C, using microwave enhancement, furnishes 2,3,4-substituted pyrrole **145** ($R=\text{Ph}$) in 80% yield. Since both reactions outlined in the Scheme 43 were conducted in chloroform, the authors [50] devised a one-pot protocol to convert **143** to **145** in 77% overall yield. This one-pot method was applied to prepare a series of fused pyrroles **145**, with various groups from aryl to alkyl in position 2 of the pyrrole ring, in rather good yields.

Shi and Gevorgyan have found that a similar type of compounds can be prepared by intramolecular Rh-catalyzed reaction of alkynyltriazoles. Most likely, the key step of the process involves a Rh-carbene-alkyne metathesis step [56].

The double bond of indoles **147** is shown to react with 1-mesyl-1,2,3-triazoles **146** via formal [3+2] cycloaddition reaction with iminocarbenoid **148** formed from **146** to provide an access to pyrroloindolines **149** [57] (Scheme 44). It is worth noting that this class of compounds is related to the pyrroloindoline alkaloids, that are an important subclass of alkaloid natural products.

Sprangler and Davies extended their research to a catalytic asymmetric synthetic method towards pyrroloindolines [57]. They have found that the use of cyclohexane as a solvent and $\text{Rh}_2(\text{S-PTAD})_4$ as a catalyst is optimal for the transformation to form pyrroloindolizines **149** in good yields and high levels of enantioselectivity. The scope of the reaction was explored with respect to the triazole **146** and indole



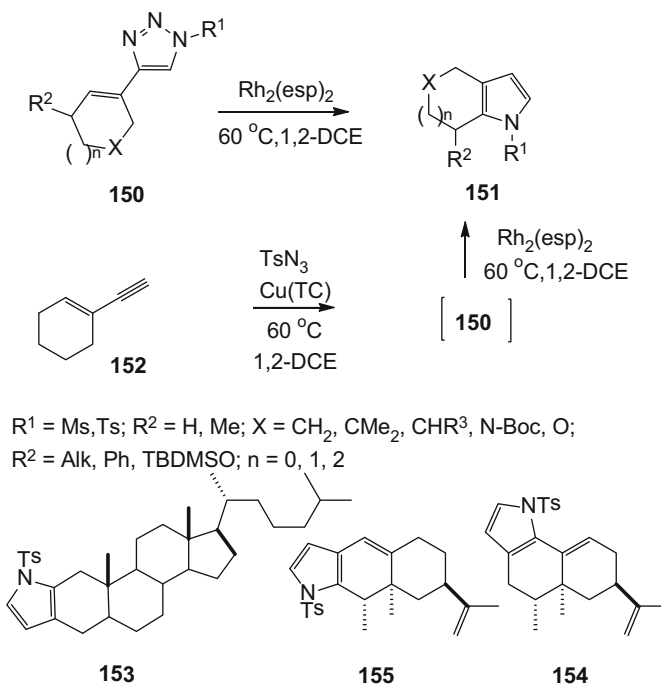
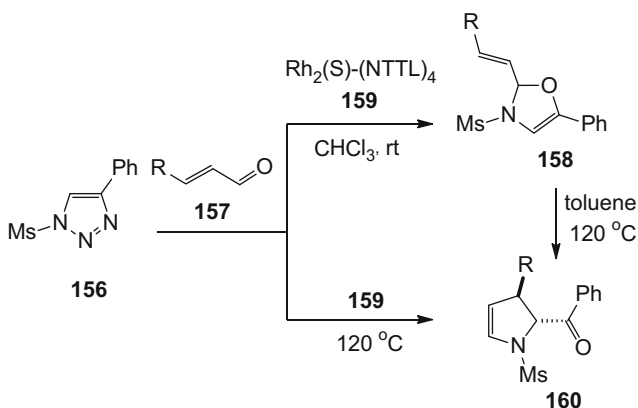
Scheme 44 Cycloaddition of azavinyl carbenoids **148** with indoles **147**

147 coupling partners (Scheme 44). Various 4-aryl substituted triazoles **146** and 3,5,6,7-monosubstituted indoles **147** are compatible with the reaction. However, the reaction was found to be sensitive to the nature of the 1-substituents in both the triazole and the benzimidazole rings: while the 1-mesyl-, ethanesulfonyl-1,2,3-triazoles **146** and 1-H, Me and allylindoles **147** provide the corresponding pyrroloindolines **149** in rather good yields and enantioselectivity, it fails for tosyl triazoles and indoles, bearing bulky and electron-withdrawing substituents at position 1 [57].

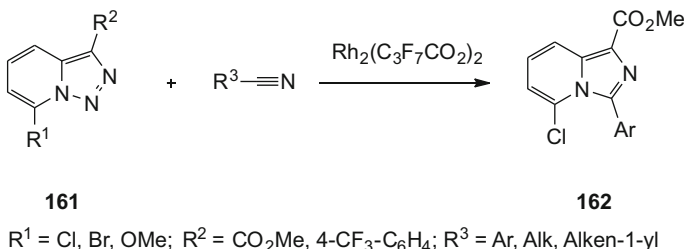
During the course of these studies, Davies and co-workers discovered that 4-cyclohexenyl-1-(sulfonyl)-1,2,3-triazoles **150** undergo a novel rhodium catalyzed intramolecular transannulation reaction to 1,2-annulated pyrroles **151** [58] (Scheme 45).

After screening several rhodium catalysts, it was found that Rh₂(esp)₂ is optimal for this transformation. The data in this report [56] allow one to conclude that the reaction is quite general. Changing the size of the cyclohexene ring, and introducing substituents to both the cyclohexene and triazole rings does not change the direction of the reaction and furnishes 1,2-fused pyrroles in good to excellent yields. Because both the synthesis of triazoles **150** and the annulation reaction can readily take place in the same solvents, the Davies group managed to realize an efficient one-pot protocol for the synthesis of bicyclic triazoles **151** in good yields (Scheme 45). The utility of the method was demonstrated by the synthesis of pyrroles **153–155** fused to the steroid derivatives of 5-cholestan-3-one and nootkatone.

The rhodium catalyzed reaction of *N*-sulfonyl-1,2,3-triazoles **156** with alkenes is a method for the synthesis of *N*-mesyl 2,3-dihydropyrroles **160** that are valuable structural fragments of various biologically active compounds. Thus, Murakami

**Scheme 45** Synthesis of fused pyrroles**Scheme 46** Transformation of *N*-mesyl-1,2,3-triazoles **156**

and colleagues have found that the reaction of *N*-mesyl-4-phenyl-1,2,3-triazole **156** with α,β -unsaturated aldehydes **157** produces trans-2,3-disubstituted dihydropyrroles **160** in good yields. Interestingly, the reaction has been carried out at room temperature, affording *N*-Ms dihydrooxazoles **158**, which in turn rearrange to dihydropyrroles **160** in toluene at 120 °C (Scheme 46) [59].



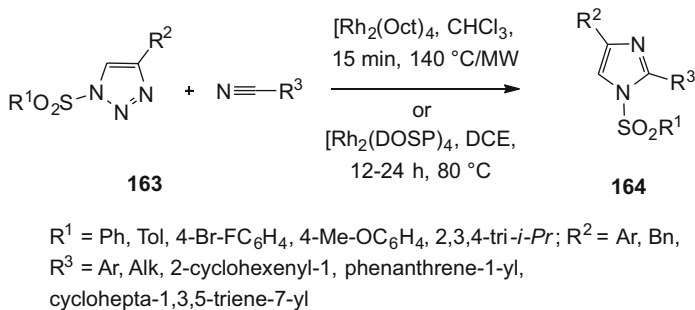
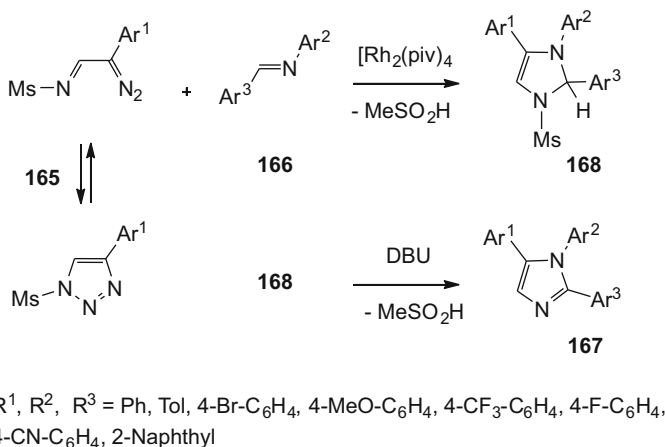
Scheme 47 Reaction of triazolopyridines **161** with nitriles

5.2 Syntheses of Imidazoles

Imidazoles are an important class of five-membered heterocycles found in a number of natural products and pharmaceutical compounds. Denitrogenative annulation reactions of pyrido-triazoles, 1-sulfonyl and 1,2,4-triazolyl-1,2,3-triazoles have recently been used for the synthesis of substituted monocyclic and fused imidazoles, as well as conjugates with other heterocyclic compounds [53, 60–63]. Together with the synthesis of pyrroles **139** described above, the Gevorgyan group developed the ring transformation reaction of triazolopyridines **161** to imidazo-pyridines **162** [53] (Scheme 47). Firstly, triazolopyridines **161** react smoothly with aryl, alkyl, and alkenyl nitriles in the presence of rhodium tetraacetate in a regioselective manner to furnish imidazo[1,5-a]pyridines **162** in good to excellent yields. The presence of electron-withdrawing groups at position 3 of triazole **161** and a halo- or methoxy group at position 7 is required for the reaction to take place.

1-Sulfonyl-1,2,3-triazoles **163** are also capable of reacting with various nitriles under treatment with rhodium catalyst to form 1,2,4-substituted imidazoles **164** in high to excellent yields [60] (Scheme 48). Both conventional and microwave heating give the same yield of the final products. A series of rhodium catalysts was examined and both rhodium(II) octanoate and $Rh_2(S-DOSP)_4$ were found to be the best. The reaction is found to be general with respect to triazole and nitrile components. Similarly to the reaction of triazolopyridine **161**, the transformation of triazoles **163** is regioselective, forming only imidazole type products **164**.

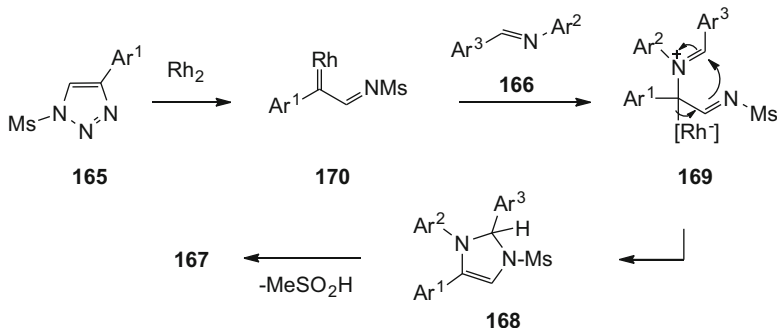
Fokin and co-workers have shown that the double bond of aldimines **166** can react with rhodium (II) azavinyl carbenes derived from *N*-mesyl triazoles **165** under heating at 120°C for 5–10 min with $Rh_2(piv)_4$ to form imidazole derivatives **167** in good yields (Scheme 49). Lowering the temperature to 40°C allowed them to isolate the intermediate imidazoline **168** that was thermally unstable and underwent elimination of sulfinic acid, restoring the aromaticity of the imidazole ring [61]. After the triazole was consumed, 1,8-diazabicycloundec-7-ene (DBU) was added and heating continued for an extra minute to enhance the final aromatization of the product formed. The reaction proceeds smoothly with different 4-aryl-1,2,3-triazoles and aldimines of aromatic aldehydes and anilines.

**Scheme 48** Synthesis of *N*-sulfonyl imidazoles**Scheme 49** Reactions of *N*-mesyl-1,2,3-triazoles **165** with aldimines **166**

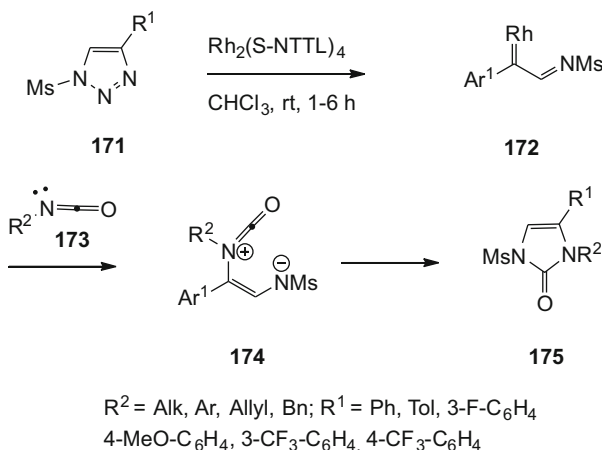
The mechanism of the reaction is presented in Scheme 50. Because imidazoline **168** has been identified, evidence is indicating that the mechanism involves an interaction of the aldimine group with the carbene center of **170** to form a zwitterion **169** which undergoes cyclization to intermediate **168**. The latter, after elimination of sulfinic acid affords the final product **167**.

The imine double bond of isocyanates **173** is shown to react with 1-sulfonyl-1,2,3-triazoles **171** via formal [3+2] cycloaddition reaction to azavinyl carbene **172**, formed from **171**, to provide an access to *N*-sulfonyl imidazolones **175** [62].

Fokin and co-workers have found that the use of *N*-mesyl-1,2,3-triazoles **171** and $\text{Rh}_2(\text{S-NTTL})_4$ gives an optimal tool to generate rhodium carbenes suitable to react smoothly and selectively with the $\text{C}=\text{N}$ bond of various isocyanates **173** to form a variety of 1,3,4-substituted imidazolones **175** in very good yields (Scheme 51). Remarkably, allyl isocyanate **173** ($\text{R}=\text{allyl}$) reacts with complete chemoselectivity, favoring ring transformation reaction over cyclopropanation of the $\text{C}=\text{C}$ double bond of the allyl group. The reaction was found as general with



Scheme 50 The plausible mechanism of transformation of **165**–**167**

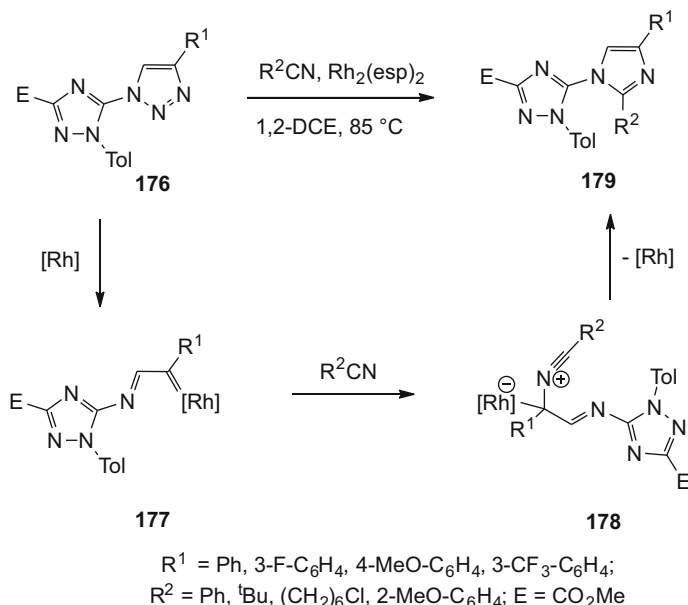


Scheme 51 Reactions of *N*-mesyl-1,2,3-triazoles with isocyanates

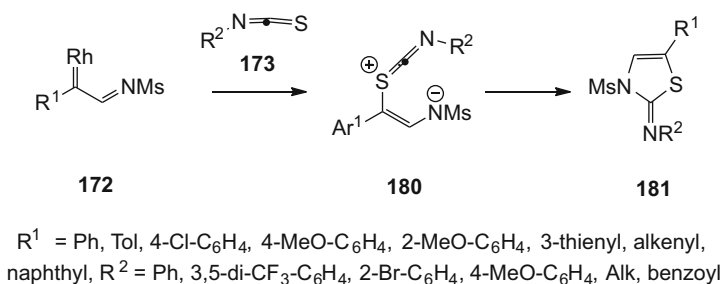
respect to substituents R^1 and R^2 in the 1,2,3-triazole and isocyanate molecules, respectively. A plausible mechanism includes the attack of the lone pair of isocyanate on the azavinyl carbene to generate a zwitterionic intermediate **174**. The latter cyclizes to an imidazole ring via heteroelectrocyclization [2] to form the final product.

Zibinsky and Fokin discovered that an electron-deficient heterocycle at the position 1 of the 1,2,3-triazole ring, similarly to sulfonyl groups, can facilitate its conversion to carbenes [63]. Thus, reaction of 1,2,4-triazolyl-1,2,3-triazoles **176** with aromatic and aliphatic nitriles in the presence of $\text{Rh}_2(\text{esp})_2$ in 1,2-DCE at 85°C provided conjugates of 1,2,4-triazole and imidazole rings **179** in 68–85% yields (Scheme 52).

This reaction is similar to the reaction of *N*-sulfonyl-1,2,3-triazoles (see above) and most likely starts with the initial attack of the nitrile nitrogen onto the electrophilic carbene center of **177** to form a zwitterionic product **178**. Subsequent cyclization of the latter to an imidazole **179** finalizes the process.



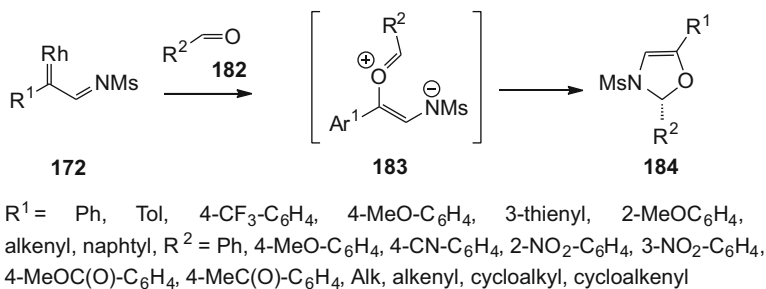
Scheme 52 Plausible mechanism of transformation of *N*-triazolyl-1,2,3-triazoles **176** to imidazoles **179**



Scheme 53 Synthesis of thiazole-2-imines **181**

5.3 Thiazoles and Oxazoles

In contrast to isocyanates, reaction of rhodium azavinylcarbenes **172** with isothiocyanates **173** is directed to the sulfur rather than the nitrogen atom of isocyanate. The generated thiocarbonyl ylide intermediate **180** undergoes cyclization to afford 2-iminothiazoles **181** (Scheme 53). Fokin and co-workers have found that the optimal conditions for the reaction of 1-sulfonyl-1,2,3-triazoles with isocyanates (vide supra) are perfectly applicable to the reaction with isothiocyanates to furnish a variety of 1-mesyl-4- and 2-iminosubstituted-thiazoles **181** in good yields



Scheme 54 Synthesis of homochiral oxazolines **184**

[62]. Exceptionally good results were achieved for the reaction of isothiocyanates bearing electron-withdrawing substituents.

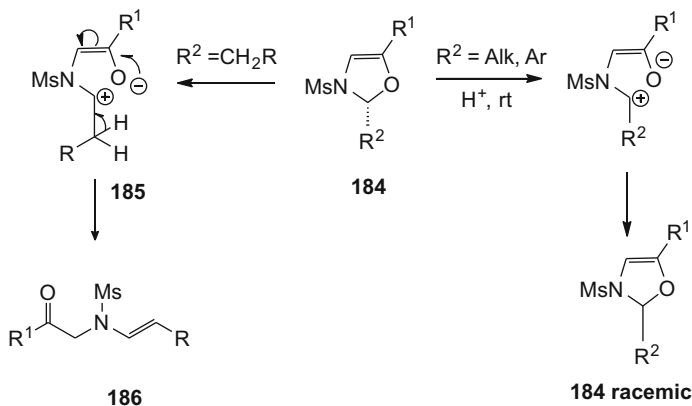
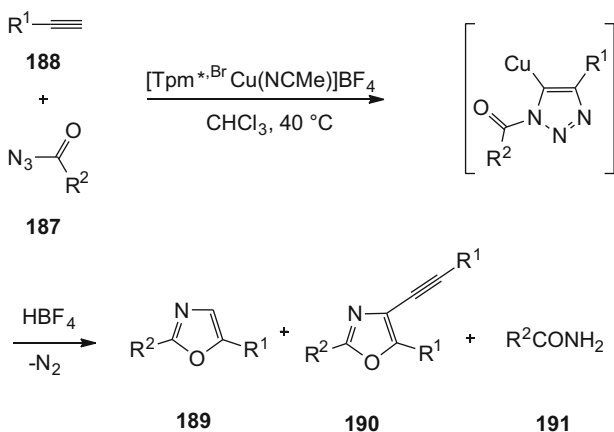
Conversely, reaction of **171** having electron-donating substituents, including both aryls and alkyls, proceeds only reluctantly; the conversion of the process is low and the yields of the thiazoles are poor. Remarkably, the reaction tolerates a large variety of 4-substituted 1,2,3-triazoles **171** as shown in Scheme 54 [62].

Carbonyl ylides **183**, generated from rhodium catalyzed decomposition of diazocarbonyl compounds with ketones are prone to react with ketones via intermolecular 1,3-dipolar cycloaddition. However, azavinylcarbenes **172** react with aldehydes **182** to generate rhodium-zwitterionic adducts that undergo an intramolecular cyclization to form homochiral 3-sulfonyl-4-oxazolines **184** in excellent yields and with high enantioselectivity [61]. Attempts of the authors [61] to trap the zwitterion **183** with reactive dipolarophiles were unsuccessful.

A variety of aromatic and aliphatic aldehydes readily react with 1-mesyl-4-aryl-1,2,3-triazoles **171**. An optimal enantioselectivity is obtained in the reaction of 1-mesyl-1,2,3-triazoles with aldehydes performed at ambient temperature in chloroform with use of $[\text{Rh}_2\{(\text{S})\text{-NTTL}\}_4]$ catalyst. A prolonged reaction time is shown to lower the enantiomeric purity of most products. This was explained by the reversible ring opening of products **184** due to the lability of the C–O bond (Scheme 55, right part).

Although various 4-aryl substituted compounds **171** (Scheme 55) react with aldehydes to provide oxazolines **184** in excellent yields and enantioselectivity, the alkyl-substituted triazoles **171** failed to provide oxazoline products. It was explained by the facile 1,2-hydride shift of the carbene **185** to form enamines **186**.

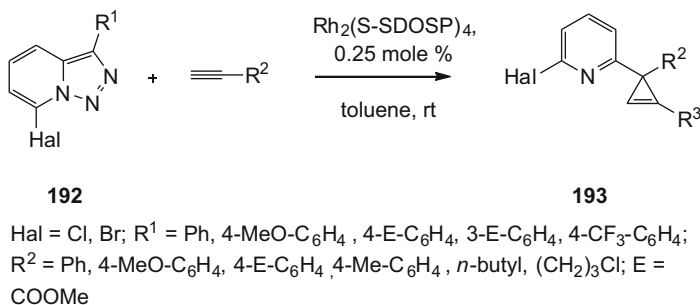
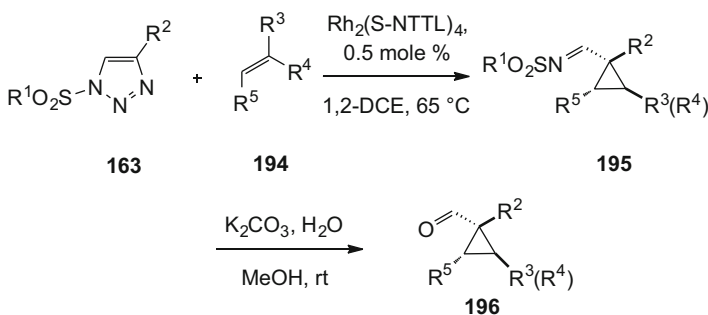
The formation of an aromatic oxazole ring occurs in the reaction of terminal alkynes with carbonyl azides in the presence of a copper catalyst. Thus Cano et al. have shown that carbonyl azides **187** react with acetylenes **188** to form a mixture of mainly oxazoles **189**, and smaller amounts of oxazol-5-yl acetylenes **190** and amides **191** (Scheme 56). The formation of these products was explained by the primary formation of a copper-triazole that undergoes evolution of dinitrogen to form the final products via a multistep process [64].

**Scheme 55** Isomerization of 4-oxazolines**Scheme 56** Synthesis and transformation of *N*-carbonyltriazoles

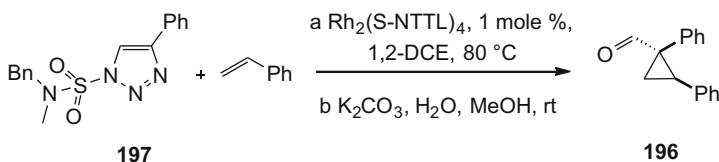
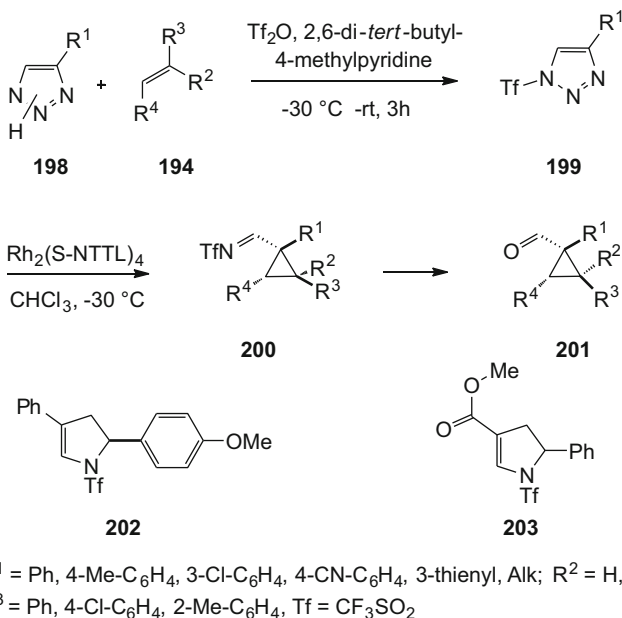
5.4 Cyclopropenes and Cyclopropanes

In contrast to the reaction of *N*-sulfonyl-1,2,3-triazoles with acetylenes, where the formation of pyrroles was observed (see above) ring transformation of 1,2,3-triazolo[1,2-*a*]pyridines **192** leads in general to a mixture of pyridyl-cyclopropenes and indoles [53, 65]. V. Gevorgyan and colleagues have found that the use of Rh₂(S-DOSP)₂ in the reaction of triazolo-pyridines **192** with acetylenes allowed to selectively prepare a variety of pyridyl-cyclopropenes **193** in good yields (Scheme 57).

Triazoles **192**, bearing both electron-withdrawing and electron-donating aryl substituents at C-3, are shown to react regioselectively with various alkyl-, aryl-, and alkenyl-containing acetylenes [65].

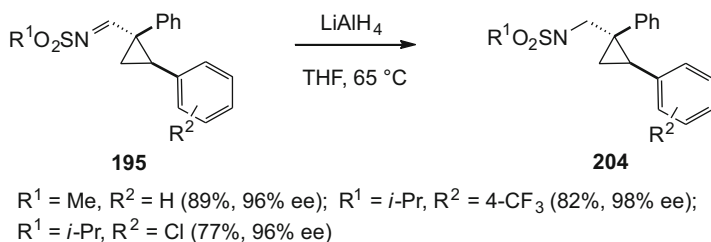
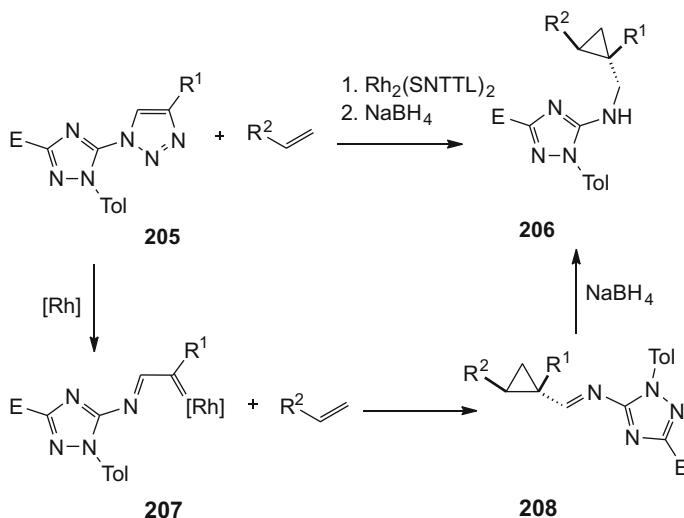
**Scheme 57** Synthesis of cyclopropenes **193****Scheme 58** Reactions of *N*-sulfonyl-1,2,3-triazoles with alkenes

The Gevorgyan and Fokin groups reported the formation of 1,2-diphenyl-cyclopropane-1-carbaldehyde **196** when *N*-tosyl-4-phenyl-1,2,3-triazole **163** was reacted with styrene in the presence of rhodium tetra-octanoate [60] (Scheme 58). A careful study for the reaction of 1-sulfonyl-1,2,3-triazoles **163** with a variety of alkenes **194** in the presence of various chiral Rh₂ complexes was made by the Fokin group [66]. The resulting sulfonamide imines **195** are not stable and were smoothly transformed into the corresponding aldehydes **196** by treatment with potassium carbonate in wet methanol. All catalysts used, namely Rh₂(S-DOSP)₄, Rh₂(S-PPTL)₄, Rh₂(S-PTAD)₄, and Rh₂(S-NTTL)₄ allowed to prepare target aldehydes **196** in very good yields, mainly with good *trans* diastereoselectivity. The enantioselectivity is found to depend on the nature of both the catalyst and sulfonyl group. The highest values of enantioselectivity (91–99%) were found in the reaction of 1-alkylsulfonyl-1,2,3-triazoles **163** (R¹=Me-, *n*-C₈H₁₇, *i*-Pr). Interestingly, the reaction of **163** (R¹=*i*-Pr, R²=Ph) with Rh₂(S-DOSP)₄ provides the opposite enantiomer, though with very low (*ee* = <16%) enantioselectivity. The study of the scope of the reaction with respect to the alkene has shown that a broad range of substituted styrenes took part in the reaction to afford aldehydes **196** in good yield and high enantioselectivity. 1-Mesyl-1,2,3-triazoles **171** with both electron-rich and electron-deficient substituents at position 4 smoothly produced 1-mesylimino-1-phenylcyclopropane **196** with excellent regioselectivity.

**Scheme 59** Reaction of sulfamoyl triazole **197** with alkenes**Scheme 60** Reaction of *N*-triflyl 1,2,3-triazoles with alkenes

Fokin and co-workers have shown that aldehyde **196** ($\text{R}^5=\text{H}$, $\text{R}^2=\text{R}^3=\text{Ph}$) can be also prepared by an alternative way by reaction of 4-Ph-1-(1,2,4-triazol-5-yl)-1,2,3-triazole **176** (its reactions with nitriles were described above) with styrene, providing a new approach to cyclopropane-4-carboxaldehydes [60]. Furthermore, this compound **196** can also be prepared from sulfamoyl triazole **197** by reaction with styrene in the presence of $\text{Rh}_2(\text{S-NTTL})_4$ followed by hydrolysis with potassium carbonate in wet methanol [67] (Scheme 59).

Very reactive 1-triflyl-1,2,3-triazoles **199** that were prepared by reaction of non-substituted 1,2,3-triazoles **198** with triflic anhydride in the presence of 2,6-di-*tert*-butyl-4-methylpyridine were used in situ in reaction with olefins in highly enantio- and diastereoselective transformations. This protocol provided a convenient access to a series of homochiral cyclopropane carboxaldehydes **201** without use of sulfonyl azides (Scheme 60). Interestingly, reactions of electron-rich 4-methoxystyrene with 5-phenyl-1,2,3-triazole and 5-ethoxycarbonyl-1,2,3-triazole

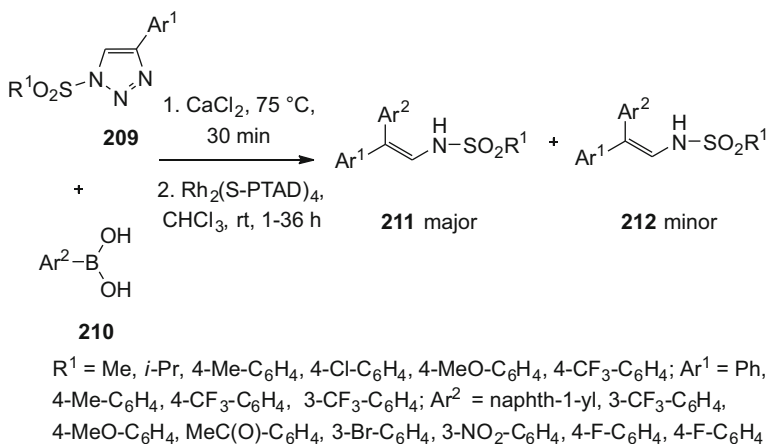
**Scheme 61** Synthesis of chiral sulfonylamino homoaminocyclopropanes **204****Scheme 62** Synthesis of chiral triazolylamino homoaminocyclopropanes **204**

with styrene proceeds by another path to give 2,3-dihydropyrroles **202** and **203** in 92% and 75% yields, respectively [68].

Because of the susceptibility of imines **195** towards hydrolysis, they were not isolated in pure form. However, fast treatment of the latter with LiAlH_4 allowed the Fokin group to provide an easy access to chiral homoaminocyclopropanes **204** (Scheme 61) [66].

Homoaminocyclopropanes **206**, bearing a 1,2,4-triazole substituent, were prepared by a one-pot synthesis from 1,2,4-triazolyl-1,2,3-triazoles after treatment with alkenes in the presence of $\text{Rh}_2(\text{S-NTTL})_4$ followed by reduction of the intermediate imine **208** to give final products in good yields with high enantioselectivity. Interestingly, the use of $\text{Rh}_2(\text{S-DOSP})_4$ and $\text{Rh}_2(\text{R-NTV})_4$ in the reaction of **205** ($\text{R}^1 = \text{R}^2 = \text{Ph}$) furnishes the opposite enantiomer **206** in 38% and 66% *ee*, respectively [62] (Scheme 62).

Cyclopropanes bearing both carboxaldehyde and disubstituted amino groups **107** were successfully synthesized thermally, without a catalyst by cyclopropanation of



Scheme 63 Synthesis of *N*-sulfonyl enamines **211** and **212**

donor/acceptor carbenes in which the donor group is a protected amine functionality (see Sect. 2) [44].

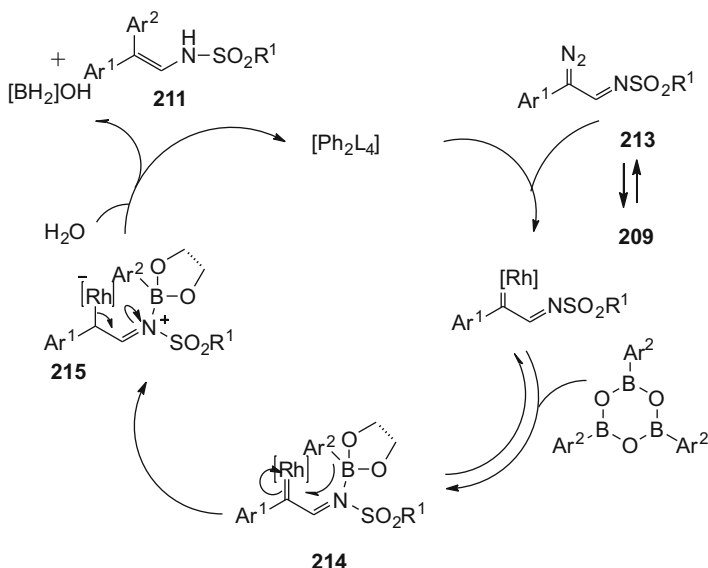
5.5 Enamines, Enaminones, and Azadienes

Enamines and enaminones are convenient chemical reagents and used in the syntheses of various classes of organic compounds. Therefore, development of new, efficient methods for their synthesis is always desirable. Fokin and co-workers demonstrated the mild, efficient rhodium and boronic acid catalyzed arylation of 1-sulfonyl-1,2,3-triazoles **209** providing a convenient access to *N*-sulfonyl enamines **211** [69]. They have found that triazoles **209** can react with boronic acids in the presence of various rhodium catalysts, optimally with $\text{Rh}_2(\text{SPTAD})_4$, and CaCl_2 as an additive to form arylated enamines **211** with high selectivity as shown in Scheme 63.

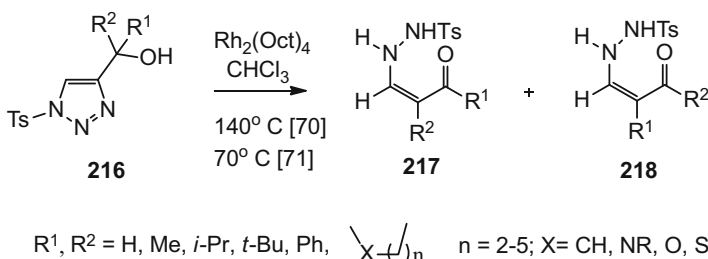
Although the arylation reaction takes place with high stereoselectivity, compounds **211** ($\text{R}^1 = \text{Me}$, $\text{R}^2 = 4\text{-Me-}$, 4-CF_3 , 3-CF_3 ; $\text{R}^3 = \text{Ph}$, 3-NO_2 , 3-CF_3 , $4\text{-Br-C}_6\text{H}_4$) were obtained contaminated with isomer **212** in 10 to 20% amount.

The formation of enamines **211** is proposed to start with the reaction of diazoimine **213**, existing in equilibrium with *N*-sulfonyl-1,2,3-triazole **209**, with a rhodium carboxylate catalyst as shown in the Scheme 64. It was proposed [69] that the lone pair of the sulfonyl imine nitrogen reversibly coordinates onto the empty orbital of the boron atom to generate complex **214**. Then, an irreversible facial-selective shift of the aryl group from boron to carbon occurs to furnish species **215**. The elimination of the rhodium catalyst and boronic acid most likely involves hydrolysis to finalize the process to form enamines **211**.

Remarkably, the Murakami and Fokin groups have published independently about the synthesis of a series of enaminones **217** accompanied by the minor isomer **218** by rhodium(II) catalyzed denitrogenative rearrangement starting from



Scheme 64 Plausible mechanism for arylation of **209**

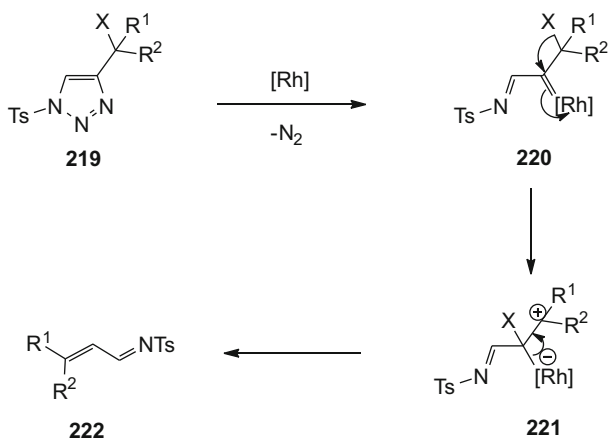
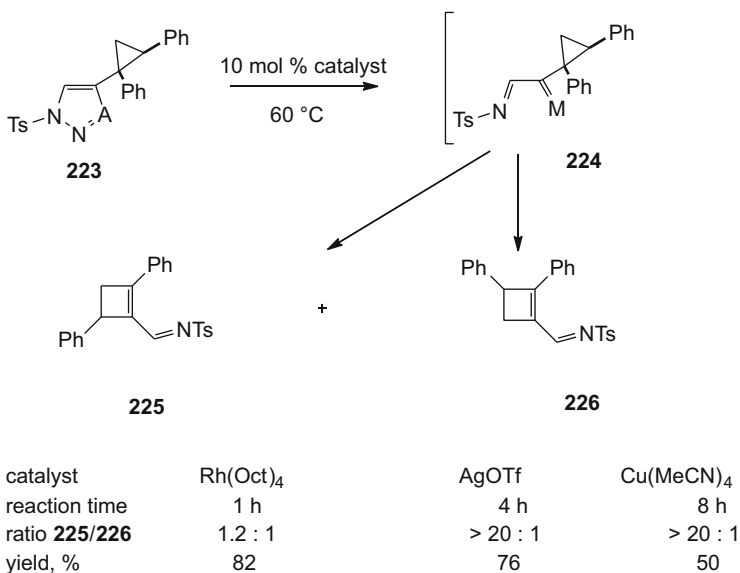


Scheme 65 Synthesis of enaminones **217** and **218**

N-sulfonyl-4-hydroxymethyl-1,2,3-triazoles of type **216** [70, 71] (Scheme 65). Moreover, a discussion on the mechanistic details together with a careful analysis of the reaction details was highlighted by Gulevich and Gevorgyan [48]. Generally, the formation of two isomeric products **217** and **218** takes place depending on which substituent migrates to the carbenium center. The migrating ability of various groups was determined and based on these data it is possible to design the selective synthesis of required compounds.

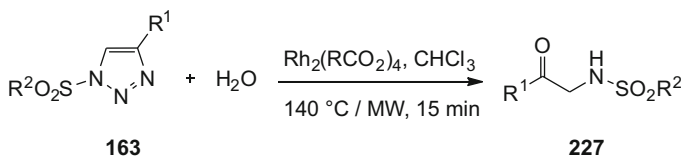
If R^1 and R^2 groups are part of a ring system, intramolecular alkyl migration occurs to form cyclic enaminones **217** with an expansion of the former cycle. Carbocyclic structures were expanded by one carbon atom to form five- to eight-membered rings in 70–99% yields [70, 71].

The formation of 1-azadienes **222** took place in similar conditions with 4-alkyl-1-sulfonyl-1,2,3-triazoles **219** (Scheme 66). Remarkably, the migration of alkyl,

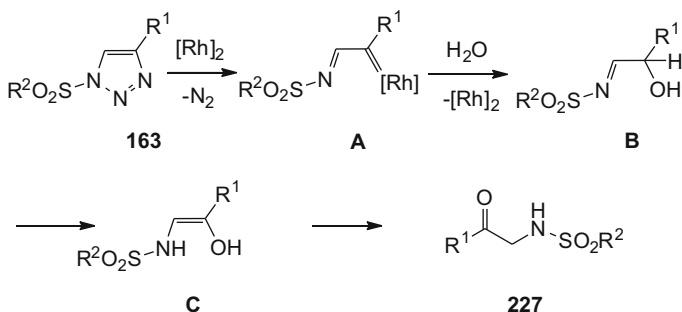
**Scheme 66** Synthesis of 1-azadienes **222****Scheme 67** Synthesis of cyclobutenes **225** and **226**

acetoxo, and piperazine groups occurs to furnish azadienes **222** in very good yields [71].

The possibility to expand a cyclopropyl to a four-membered ring was demonstrated by Tang et al. by carrying out the reaction of 4-cyclopropyl-1-tosyl-1,2,3-triazoles **223** with metal catalysts at 60°C [72] (Scheme 67). Although Rh₂(Oct)₄ is the most reactive, AgOTf and Cu(MeCN)₄PF₆ catalysts provide higher selectivity for the formation of cyclobutene **225** over cyclobutene **226**.



Scheme 68 Synthesis of aminoketones **227**



Scheme 69 Plausible mechanism for the formation of aminoketones **227** from *N*-sulfonyl-1,2,3-triazoles and water

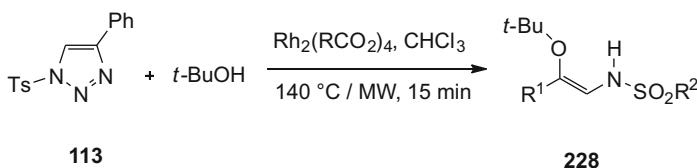
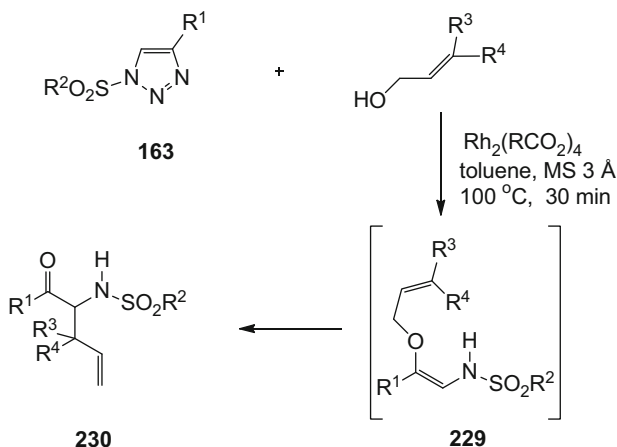
5.6 α -Aminoketones

The Murakami group examined various catalysts for the reaction of 4-aryl-1-(*N*-tosyl)-1,2,3-triazoles **163** and found that the insertion of the α -iminometal carbenoid into the O–H bond of water took place after use of rhodium catalyst to form α -aminoketones of type **227** (Scheme 68). In general, the reaction tolerates both a 4-substituent and substituents on the sulfonyl group. Various 4- and 1-sulfonyl triazoles **163** react with rhodium tetraacetate in chloroform under microwave conditions at 140°C to furnish aminoketones **227** in high yields [73].

A plausible mechanism is depicted in Scheme 69. Initially, a denitrogenative process occurs to generate α -imino rhodium carbenoid **A**. Insertion of **A** into the O–H bond of water leads to the formation of α -iminoalcohol **B** and release of rhodium catalyst. Finally, imine-enamine tautomerism followed by keto-enol tautomerism of enol **C** affords α -aminoketones **227**.

Interestingly, 4-phenyl-*N*-tosyl triazole **113** can also react with *tert*-butyl alcohol to form α -amino enol ether **228**, most probably via carbenoid insertion followed by imine-enamine tautomerization [73] (Scheme 70).

Conversely, reaction of compound **163** with allylic alcohol led to the formation of another type of products, α -allyl- α -aminoketones **230**. The process for formation of the latter most probably involves the Claisen rearrangement of initially formed allyl enol ether **229** (Scheme 71) [74].

**Scheme 70** Synthesis of α -amino enol ether **228**

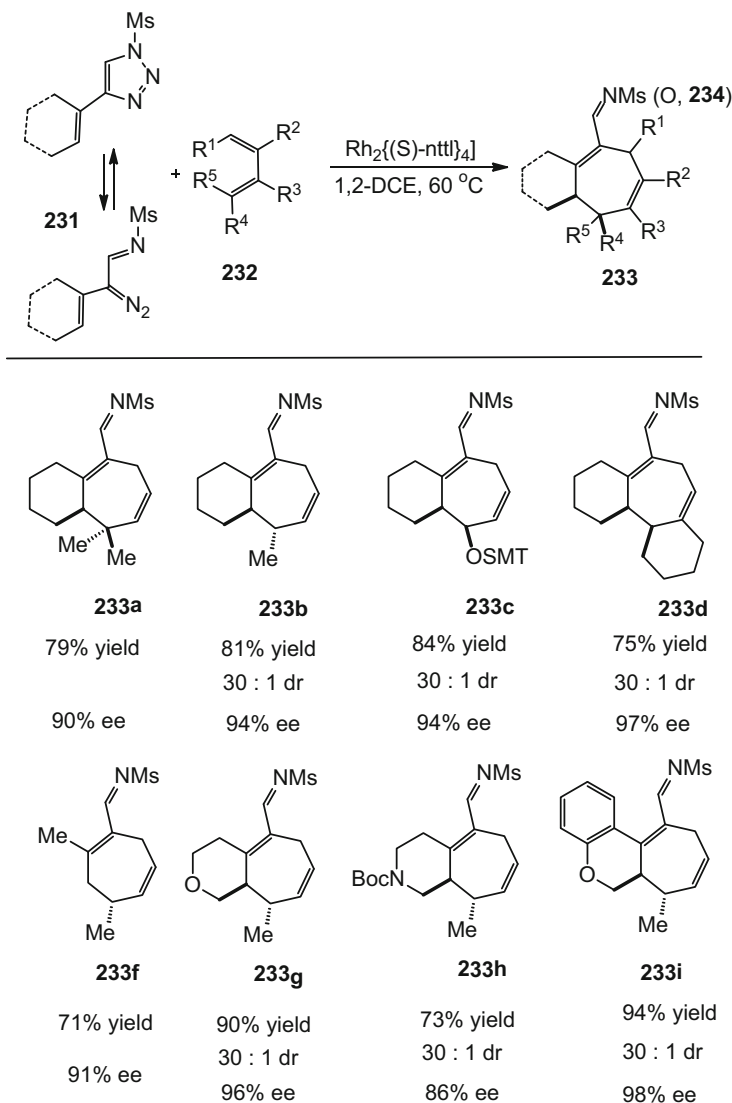
$\text{R}^1 = \text{Ph}, 4\text{-Me-C}_6\text{H}_4, 4\text{-CF}_3\text{-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4, 4\text{-EtO}_2\text{C}_6\text{H}_4, 4\text{-Ph-C}_6\text{H}_4, 3\text{-thienyl}, 1\text{-cyclohexenyl}, \text{Alkyl}, \text{H}; \text{R}^2 = \text{Me}, \text{Alkyl}, 4\text{-Br-C}_6\text{H}_4, 4\text{-MeO-C}_6\text{H}_4, 4\text{-Me-C}_6\text{H}_4; \text{R}^3, \text{R}^4 = \text{H}, \text{Me}$

Scheme 71 Synthesis of sulfonamide **230**

The Murakami group managed to combine the synthesis of α -allyl- α -amino ketones **230** with a process for the preparation of triazole **163** from terminal acetylenes and azides. Thus they introduced an extremely facile one-pot method to convert terminal alkynes into α -allyl- α -amino ketones through triazoles and vinyl ether intermediates.

5.7 Cycloheptadienes

There is a single paper recently published by the Davies group where formal [4+3] cycloaddition of dienes **231** to rhodium butadienyl aza carbenoid, generated from 4-alkenyl-1-*N*-sulfonyl-1,2,3-triazoles **231**, occurred to afford a series of 1,4-cycloheptadienes **233** in good yields and high enantio- and diastereoselectivity.



Scheme 72 The scope for the reaction of 4-alkenyl-1,2,3-triazoles **231** with dienes **232**

The reaction discovered is general for a broad range of both participants, 4-alkenyl-1-mesyl-1,2,3-triazoles **231** and 1,3-dienes **232**, enabling a stereoselective synthesis of polycyclic imines (Scheme 72) [75]. Furthermore, reaction of 4-alkenyl-1,2,3-triazoles **231** with dienes **230** followed by basic hydrolysis was shown to afford α,β -unsaturated aldehyde **233** in high yield with no observable epimerization.

5.8 Addendum

Syntheses of fused dihydropyrroles [76], sulfonamides [77], *N*-sulfonylamidines [78], and fused indoles [79] were published in the early beginning of 2014 based on the denitrogenative transformation of 1-*N*-sulfonyl-1,2,3-triazoles.

6 Conclusions

Both rearrangements and metal catalyzed transformations of 1,2,3-triazoles are possible because an equilibrium exists between diazoimine and 1,2,3-triazole isomeric forms. The intermediate diazoimine can be intramolecularly trapped by an electrophilic center to give other heterocyclic compounds. On the other hand, an attack of metal catalysts (Rh, Ru, Ni et al.) onto the diazo group of these diazoimines is accompanied by dinitrogen elimination to form an azavinyl carbenoid. The latter can be involved either in cycloaddition to a multiple bond or in an insertion into C–H, C–C, N–H, or O–H bonds to form a variety of heterocycles and other valuable organic compounds such as cyclopropanes, cyclopropenes, enamines, and diazadienes.

Acknowledgments Vasily Bakulev and Tetyana Beryozkina thank Russian Foundation for Basic Research (14-03-01033) and State task of Ministry Education No 4.1626.2014/K. Wim Dehaen thanks the FWO-Vlaanderen and the University of Leuven for financial support.

References

1. Taylor EC, Turchi IJ (1979) 1,5-Dipolar cyclizations. *Chem Rev* 79:182–231
2. Bakulev VA, Kappe CO, Padwa A (1996) Application of the 1,5-electrocyclic reaction in heterocyclic synthesis. In: Hudlicky T (ed) *Organic synthesis: theory and applications*, vol 3. JAI Press, Greenwich, pp 149–229
3. Haron RE, Stanley JF, Gupta SK et al (1970) *N,N*-Dialkylamino-1,2,3-triazole- α -diazoamidines tautomers from substituted benzenesulfonyl azides and ynamines. *J Org Chem* 35:3444–3448
4. Hermes ME, Marsh FD (1967) 1-Cyano-1,2,3-triazole- α -diazo-*N*-cyanoimine tautomers from cyanogen azide and acetylenes. *J Am Chem Soc* 89:4760–4764
5. Birney DM, Ham S, Unruh GR (1997) Pericyclic and pseudopericyclic thermal cheletropic decarbonylations: when can a pericyclic reaction have a planar, pseudopericyclic transition state? *J Am Chem Soc* 119:4509–4517
6. Fabian WMF, Bakulev VA, Kappe CO (1998) Pericyclic versus pseudopericyclic 1,5-electrocyclization of iminodiazomethanes. An ab initio and density functional theory study. *J Org Chem* 63:5801–5805
7. Dimroth O (1904) Über desmotrope Verbindungen. *Ann Chem* 335:1–35
8. Morzherin YY, Kolobov MY, Mokrushin VS et al (2000) Heterocyclization of compounds containing diazo and cyano groups. 6. Theoretical and experimental investigations of cyclization of 2-cyano-2-diazoacetamides to 5-hydroxy-1,2,3-triazole-4-carbonitriles. *Chem Heterocycl Compd* 36:22–36

9. Morzherin YY, Subbotina YO, Nein YI et al (2004) Synthesis and heteroelectrocyclization of unsymmetrically substituted diazomalonamides. *Russ Chem Bull* 53:1305–1310
10. Alkorta I, Blanco F, Elguero J et al (2010) The azido-tetrazole and diazo-1,2,3-triazole tautomerism in six-membered heteroaromatic rings and their relationships with aromaticity: azines and perimidine. *Tetrahedron* 66:2863–2868
11. L'abbé G (1984) Molecular rearrangements of five-membered ring heteromonocycles. *J Heterocycl Chem* 21:627–638
12. Wamhoff H (1984) 1,2,3-Triazoles and their benzo derivatives. In: Katritzky AR, Rees SW, Potts KT(eds) *Comprehensive heterocyclic chemistry I*, vol 4.11. Pergamon, Oxford, pp 670–732
13. Fan W-Q, Katritzky AR (1996) 1,2,3-Triazoles. In: Katritzky AR, Rees SW, Scriven EFV, Storr RC (eds) *Comprehensive heterocyclic chemistry II*, vol 4.01. Pergamon, Oxford, pp 1–126
14. L'abbé G (1990) Molecular rearrangements of 1,2,3-triazoles and 1,2,3-thiadiazoles. *Bull Soc Chim Belg* 99:281–291
15. Morzherin YY, Pospelova TA, Gluhareva TV et al (2004) The Dimroth rearrangement of 1,2,3-triazoles in the synthesis of anion receptors based on calix[4]arenes. *ARKIVOC* 11:31–35
16. Uher M, Knopova V, Martvin A (1979) Dimroth rearrangement in the thiadiazole-triazole system. *Chem Zvesty* 10:514–520
17. Bakulev VA, Dehaen W (2004) *The chemistry of 1,2,3-thiadiazoles*. John Wiley & Sons, Inc, Hoboken
18. L'abbé G, Bruynseels R, Delbeke P et al (1990) Molecular rearrangements of 4-iminomethyl-1,2,3-triazoles. Replacement of 1-aryl substituents in 1H-1,2,3-triazole-4-carbaldehydes. *J Heterocycl Chem* 27:2021–2027
19. L'abbé G, Vandendriessche A (1989) Ring-degenerate rearrangement of 5-amino-4-iminomethyl-1, 2, 3-triazoles. *J Heterocycl Chem* 26:701–703
20. L'Abbé G, Van Essche G, Delbeke P et al (1990) Rearrangements of 1-phenyl-1,2,3-triazoles bearing a hydrazine or oxime function at the 4-position. *Bull Soc Chim Belg* 99:833–834
21. Dehaen W, Becher J (1993) Ring opening of five-membered heteroaromatic azides and nitrenes. *Acta Chem Scand* 47:244–254
22. Bakulev VA, Lebedev AT, Dankova EF et al (1989) Two directions of cyclization of α -diazoo- β -dithioamides. New rearrangements of 1,2,3,-triazole-4-carbothiamides. *Tetrahedron* 45:7329–7340
23. Katritzky AR, Ji FB, Fan WQ et al (1992) Novel Dimroth rearrangements of the benzotriazole system: 4-amino-1-(arylsulfonyl)benzotriazoles to 4-[(arylsulfonyl)amino]benzotriazoles. *J Org Chem* 57:191–195
24. Temple DH, Smith JA, Montgomery JA (1972) Preparation and properties isomeric v-triazolopyridines. 1- and 3-Deaza-8-azapurines. *J Org Chem* 37:3784–3788
25. L'abbé G, Dehaen W (1988) Synthesis and thermal rearrangement of 5-diazomethyl-1,2,3-triazoles. *Tetrahedron* 44:461–469
26. L'abbé G, Dehaen W (1987) Synthesis and thermolysis of 4-methoxycarbonyl-5-(α -methoxycarbonyldiazomethyl)-1,2,3-triazoles. *Bull Soc Chim Belg* 96:823–824
27. L'abbé G, Van Stappen P, Toppet S (1985) Molecular rearrangements of 5-azido substituted 1,2,3-triazoles. *Tetrahedron* 41:4621–4631
28. L'abbé G, Beenaerts L (1989) Thermal rearrangement of 1-substituted 5-azido-4-cyano-1H-1,2,3-triazoles. *Bull Soc Chim Belg* 98:421–422
29. L'abbé G, Vandendriessche A, Toppet S (1988) Synthesis and thermolysis of 4-substituted 5-azido-1-phenyl-1,2,3-triazoles. *Tetrahedron* 44:3617–3626
30. L'abbé G, Beenaerts L (1989) Influence of electron-withdrawing N-1 substituents of the thermal behavior of 5-azido-1,2,3-triazoles. *Tetrahedron* 45:749–756
31. L'abbé G, Vercauteren K, Dehaen W (1994) Thermolysis of 4-heteroaryl substituted 5-azido-1H-1,2,3-triazoles: competition between rearrangement and decomposition. *Bull Soc Chim Belg* 103:321–327

32. Moderhack D, Beissner A (1997) Conversion of *N*-(1,2,3-triazolyl)hydrazonoyl bromides into functionalized 1,2,4-triazoles. *J Prakt Chem Chem Zeit* 339:582–586
33. Gilchrist TL, Gymer GE, Rees CW (1975) Reactive intermediates. Part XXIV. 1H-Azirine intermediates in the pyrolysis of 1H-1,2,3-triazole. *J Chem Soc Perkin Trans* 1:1–8
34. Gilchrist TL, Gymer GE, Rees CWJ (1971) Mechanism of the pyrolysis of 1,2,3-triazoles. 1H-Azirines as intermediates. *Chem Soc D Chem Commun* 1519–1520
35. Mitchell G, Rees CW (1987) Photolysis of 1-aryl -1,2,3-triazoles; rearrangement via 1H-azirines. *J Chem Soc Perkin Trans* 1:413–422
36. Gilchrist TL, Gymer GE, Rees CWJ (1973) Reactive intermediates. Part XXIII. Pyrolysis of 1-phthalimido-1,2,3-triazoles: formation and thermal reactions of 2H-azirines. *Chem Soc Perkin Trans* 1:555–561
37. Meza-Avina ME, Patel MK, Croatt MP (2013) Exploring the reactivity of 1,5-disubstituted sulfonyl-triazoles: thermolysis and Rh(II)-catalyzed synthesis of α -sulfonyl nitriles. *Tetrahedron* 69:7840–7846
38. Fullon BE, Wentrup C (1996) Imidoalkene-oxoketenimine interconversion. Rearrangement of a carbomethoxyketenimine to a methoxyimidoalkene and 2-methoxy-4-quinolone. *J Org Chem* 61:1363–1368
39. Clarke D, Mares RW, McNab H (1993) A novel entry to the imidoalkene-oxoketenimine energy surface. *J Chem Soc Chem Commun* 1026–1027
40. Rao VVR, Wentrup C (1998) Synthesis of aminoquinolones from triazoles via carboxamido-ketenimine and amidinoketenimine intermediate. *J Chem Soc Perkin Trans* 1:2583–2586
41. Rachwal S, Katritzky AR (2008) 1,2,3-Triazoles. In: Katritzky AR, Ramsden CA, Scriven EFV, Taylor RJK (eds) *Comprehensive heterocyclic chemistry III*, vol 5.01. Pergamon, Oxford, pp 1–158
42. Lucero PL, Pelaez WJ, Riedl Z et al (2012) Flash vacuum pyrolysis of azolylacroleins and azolylbutadienes. *Tetrahedron* 68:1299–1305
43. Rees CW, Yue T-Y (2001) Conversion of enamines, enamides and triazoles by trithiazyl trichloride into 1,2,5-thiadiazole. *J Chem Soc Perkin Trans* 1:662–667
44. Alford JS, Davies HML (2012) Expanding the scope of donor/acceptor carbenes to N-phthalimido donor groups: diastereoselective synthesis of 1-cyclopropane α -amino acids. *Organic Lett* 14:6020–6023
45. Tornøe CW, Christensen C, Meldal M (2002) Peptidotriazoles on solid phase: [1,2,3]-triazoles by regioselective copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J Org Chem* 67:3057–3064
46. Rostovtsev VV, Green LG, Fokin VV et al (2002) A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective “ligation” of azides and terminal alkynes. *Angew Chem Int Ed* 41:2596–2599
47. Chattopadhyay B, Gevorgyan V (2012) Transition-metal-catalyzed denitrogenative transannulation: converting triazoles into other heterocyclic systems. *Angew Chem Int Ed* 51:862–872
48. Gulevich AV, Gevorgyan V (2013) Versatile reactivity of rhodium-iminocarbenes derived from N-sulfonyl triazoles. *Angew Chem Int Ed* 52:1371–1373
49. Miura T, Yamauchi M, Murakami M (2009) Nickel-catalysed denitrogenative alkyne insertion reactions of N-sulfonyl-1,2,3-triazoles. *RCS Chem Commun* 1470–1471
50. Chattopadhyay B, Gevorgyan V (2011) Rh-Catalyzed transannulation of N-tosyl-1,2,3-triazoles with terminal alkynes. *Organic Lett* 13:3746–3749
51. Miura T, Hiraga K, Biyajima T et al (2013) Regiocontrolled synthesis of polysubstituted pyrroles starting from terminal alkynes, sulfonyl azides and allenes. *Organic Lett* 15:3298–3301
52. Parr BT, Green SA, Davies HML (2013) Rhodium-catalyzed conversion of furans to highly functionalized pyrroles. *J Am Chem Soc* 135:4716–4718
53. Chuprakov S, Hwang FW, Gevorgyan V (2007) Rh-Catalyzed transannulation of pyridotriazoles with alkynes and nitriles. *Angew Chem Int Ed* 46:4757–4759

54. Nakamura I, Nemoto T, Shiraiwa N et al (2009) Palladium-catalyzed indolization of *N*-arylbenzotriazoles with disubstituted alkynes. *Organic Lett* 11:1055–1058
55. Schultz EE, Sarpong R (2013) Application of in situ-generated Rh-bound trimethylenemethane variants to the synthesis of 3,4-fused pyrroles. *J Am Chem Soc* 135:4696–4699
56. Shi Y, Gevorgyan V (2013) Intramolecular transannulation of alkynyl triazoles via alkyne-carbene metathesis step: access to fused pyrroles. *Organic Lett* 15:5394–5396
57. Spangler JE, Davies HML (2013) Catalytic asymmetric synthesis of pyrroloindolines via a rhodium(II)-catalyzed annulation of indoles. *J Am Chem Soc* 135:6802–6805
58. Alford JS, Spangler JE, Davies HML (2013) Conversion of cyclic ketones to 2,3-fused pyrroles and substituted indoles. *J Am Chem Soc* 135:11712–11715
59. Miura T, Tanaka T, Hiraga K et al (2013) Stereoselective synthesis of 2,3-dihydropyrroles from terminal alkynes, azides and α , β -unsaturated aldehydes via *N*-sulfonyl-1,2,3-triazoles. *J Am Chem Soc* 135:13652–13655
60. Horneff T, Chuprakov S, Chernyak N et al (2008) Rhodium-catalyzed transannulation of 1,2,3-triazoles with nitriles. *J Am Chem Soc* 130:4972–4974
61. Zibinsky M, Fokin VV (2013) Sulfonyl-1,2,3-triazoles: convenient synthones for heterocyclic compounds. *Angew Chem Int Ed* 52:1507–1510
62. Chuprakov S, Kwok SW, Fokin VV (2013) Transannulation of 1-sulfonyl-1,2,3-triazoles with heterocumulenes. *J Am Chem Soc* 135:4652–4655
63. Zibinsky M, Fokin VV (2011) Reactivity of *N*-(1,2,4-triazolyl)-substituted 1,2,3-triazoles. *Organic Lett* 13:4870–4872
64. Cano I, Álvarez EM, Nicasio MC et al (2011) Regioselective formation of 2,5-disubstituted oxazoles via copper(I)-catalyzed cycloaddition of acyl azides and 1-alkynes. *J Am Chem Soc* 133:191–193
65. Chuprakov S, Gevorgyan V (2007) Regiodivergent metal-catalyzed rearrangement of 3-iminocyclopropenes into *N*-fused heterocycles. *Organic Lett* 9:4463–4466
66. Chuprakov S, Kwok SW, Zhang L et al (2009) Rhodium-catalyzed enantioselective cyclopropanation of olefins with *N*-sulfonyl 1,2,3-triazoles. *J Am Chem Soc* 131:18034–18035
67. Culhane JC, Fokin VV (2011) Synthesis and reactivity of sulfamoyl azides and 1-sulfamoyl-1,2,3-triazoles. *Organic Lett* 13:4578–4480
68. Grimster N, Zhang L, Fokin VV (2010) Synthesis and reactivity of rhodium(II) *N*-triflyl azavinyl carbenes. *J Am Chem Soc* 132:2510–2511
69. Selander N, Worrell BT, Chuprakov S et al (2012) Arylation of rhodium(II) azavinyl carbenes with boronic acids. *J Am Chem Soc* 134:14670–14673
70. Miura T, Funakoshi Y, Morimoto M et al (2012) Synthesis of enamines by rhodium-catalyzed denitrogenative rearrangement of 1-(*N*-sulfonyl-1,2,3-triazol-4-yl)alkanols. *J Am Chem Soc* 134:17440–17443
71. Selander N, Worrell BT, Fokin VV (2012) Ring expansion and rearrangements of rhodium(II) azavinyl carbenes. *Angew Chem Int Ed* 51:13054–13057
72. Liu R, Zhang M, Winston-McPherson G et al (2013) Ring expansion of alkynyl cyclopropanes to highly substituted cyclobutenes via a *N*-sulfonyl-1,2,3-triazole intermediate. *RSC Chem Comm* 49:4376–4378
73. Miura T, Biyajima T, Fujii T et al (2012) Synthesis of α -amino ketones from terminal alkynes via rhodium-catalyzed denitrogenative hydration of *N*-sulfonyl-1,2,3-triazoles. *J Am Chem Soc* 134:194–196
74. Miura T, Tanaka T, Biyajima T et al (2013) One-pot procedure for the introduction of three different bonds onto terminal alkynes through *N*-sulfonyl-1,2,3-triazole intermediates. *Angew Chem Int Ed* 52:3883–3886
75. Parr BT, Davies HML (2013) Rhodium-catalyzed tandem cyclopropanation/cope rearrangement of 4-alkenyl-1-sulfonyl-1,2,3-triazoles with dienes. *Angew Chem Int Ed* 52:10044–10047

76. Miura T, Funahoshi Y, Murakami M (2014) Intramolecular dearomatizing [3+2] annulation of α -imino carbenoids with aryl ring furnishing 3,4-fused indole skeletons. *J Am Chem Soc* 136:2272–2275
77. Chuprakov S, Worrell BT, Selander N et al (2014) Stereoselective 1,3-insertions of rhodium (II) azavinyl carbenes. *J Am Chem Soc* 136:195–202
78. Xing Y, Sheng G, Wang J (2014) Preparation of triazoloindoles via tandem copper catalysis and their utility as α -imino rhodium carbene precursors. *Organic Lett* 16:1244–1247
79. Yao B, Shen C, Liang Z (2014) Copper-catalyzed reaction of ketenimine and in situ generated immonium ion: access to α , β -unsaturated amidines. *J Org Chem* 79:936–942

Top Heterocycl Chem (2015) 40: 51–116

DOI: 10.1007/7081_2014_125

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Published online: 28 March 2014

Synthesis of 2*H*-1,2,3-Triazoles

Nataliya Belskaya, Julia Subbotina, and Svetlana Lesogorova

Abstract This chapter gives an overview of methods for the synthesis of NH- and N(2)-substituted 1,2,3-triazoles, their advantages, lacks, scope, and limitations. Moreover, it will give some insights on the reaction mechanisms and will explain how different conditions and structure substrates can influence the direction for reactions. An extensive analysis for the last 20 years (starting at 1990) of NH-1,2,3-triazoles chemistry is presented. Some older data with high importance are also included.

Keywords Alkylation · Arylation · Azide · Cycloaddition · Oxidative cyclization · Rearrangement · Regioselectivity

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Abbreviation

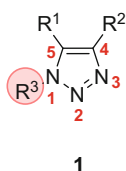
Ac	Acetyl
anhyd	Anhydrous
Ar	Aryl
B3LYP	Becke three-parameter, Lee–Yang–Parr
Bn	Benzyl
Bu	Butyl
cat	Catalyst
COSMO	Conductor-like Screening MOdel
Cy	Cyclohexyl
d	Day(s)
dba	Dibenzylideneacetone
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DFT	Density Functional Theory
DIPA	Diisopropyl amine
DMA	Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dppp	1,3-Bis(diphenylphosphino)propane
EDG	Electron-donating group
equiv	Equivalent(s)
EWG	Electron-withdrawing group
Fc	Ferrocenyl
GIAO	Gauge Independent Atomic Orbital
h	Hour(s)

Hex	Hexyl
HMBC	Heteronuclear Multiple Bond Coherence
<i>i</i> -Pr	<i>Iso</i> -propyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl)amide
LHMDS	Lithium hexamethyldisilazide lithium bis(trimethylsilyl)amide
min	Minute(s)
mol	Mole(s)
MW	Microwave irradiation
NICS	Nucleus Independent Chemical Shifts
NMP	<i>N</i> -methylpyridine
NOE	Nuclear Overhauser effect
Ph	Phenyl
Pr	Propyl
Pv	Pivaloyl
py	Pyridine
rt	Room temperature
SFC	Solvent free condition
SPS	Solid-phase synthesis
TBAF	Tetrabutylammonium fluoride
<i>t</i> -Bu	<i>Tert</i> -butyl
Tf	Trifluoromethanesulfonyl (triflyl)
THF	Tetrahydrofuran
THP	Tetrahydropyran-2-yl
TMS	Trimethylsilyl
Tp	Tetrazole
Ts	Tosyl 4-toluenesulfonyl
XRD	X-ray diffraction

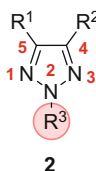
1 Introduction

1,2,3-Triazoles can be divided into three groups depending on the position of substituent at nitrogen atom [1–6]:

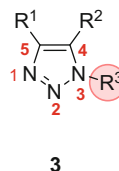
1*H*-1,2,3-Triazole



2*H*-1,2,3-Triazole

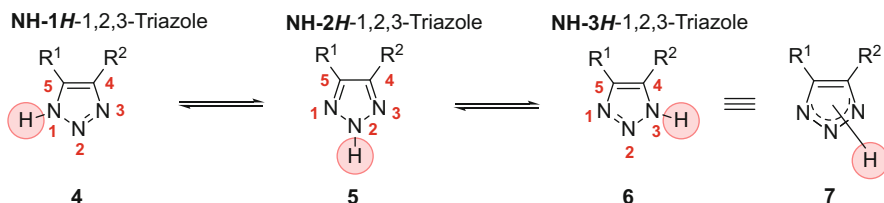


3(1)*H*-1,2,3-Triazole



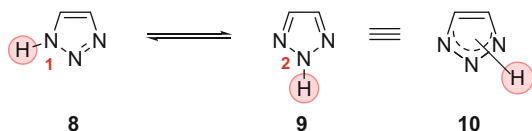
The third isomer **3**, which formally may be named as 3(1)*H*-1,2,3-triazole, was obtained in rare cases (see paragraph 4).

Triazoles **4–6** with unsubstituted ring nitrogen atom have special interest due to their importance for the synthesis of new derivatives. NH-triazoles **4–6** are thermodynamically stable tautomers. They exist in equilibrium in solutions and have very close values of Gibbs energy [1, 2, 6–12]. The ratio of tautomeric forms **4–6** can be determined by spectral methods, although it is impossible to separate them. In modern books it is a common practice not to put a certain form of tautomer to represent NH-1,2,3-triazoles, but rather to use generalized formulas, for example **7** or **10**.



Theoretical calculations of magnetic properties of NH-1,2,3-triazoles performed at B3LYP/6-311++G(d,p) level within GIAO approach confirmed the aromatic character of these *6e*-heterocycles. Nucleus independent chemical shifts (NICS) (1) calculated above the ring centers were -13.51 ppm for tautomers **8** and -13.61 ppm for **9** [7].

Experimental and theoretical studies indicated that the tautomer **8** is more stable in solution, while *2H*-isomer **9** is more stable in gas phase (~ 4.0 kcal mol $^{-1}$) [7–12].

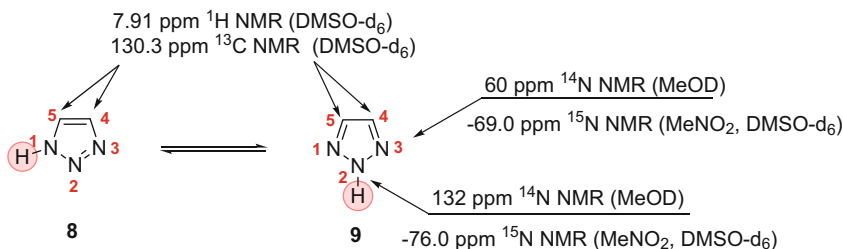
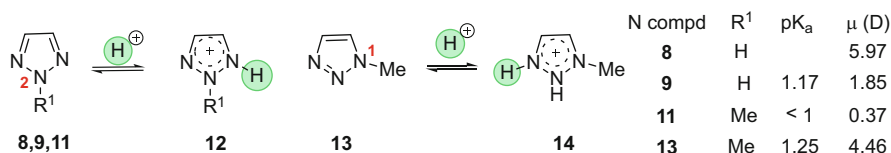
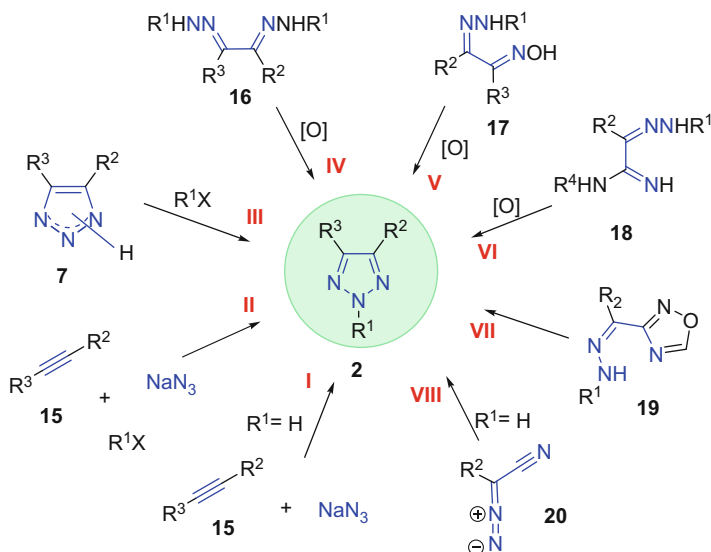


Spectroscopic ^{14}N and ^{15}N NMR data revealed that unsymmetrical 1,2,3-triazoles **4–5** exist in the *2H*-tautomer form (70–100%) [13, 14]. ^1H , ^{13}C , ^{15}N and ^{14}N NMR shifts were identical for the two hydrogen and carbon atoms in positions 4 and 5 and nitrogen atoms at positions 1, 2 and 3 of 1,2,3-triazoles for both tautomers (Scheme 1) [1, 2, 6, 9].

N-Substituted isomers of *1H* and *2H*-1,2,3-triazoles can be differentiated based on their polarity. Indeed, the dipole moment of the *1H*-isomer is substantially higher than for *2H*-1,2,3-triazoles (Scheme 2) [1, 2, 6].

1,2,3-Triazoles demonstrate amphoteric properties and can behave as a weak base or a weak acid similar to phenol. 2-Methyltriazole **11** shows a much weaker basicity in comparison with 1-methyl-1,2,3-triazole **13** (Scheme 2) [1, 3, 6, 9–14].

1,3-Dipolar cycloaddition of substituted azides to alkynes is a common approach to obtain various N(1)-derivatives of 1,2,3-triazoles. Huisgen was the first one to establish mechanistic details underlying this reaction [15]. The groups of Sharpless et al. [16] and Meldal et al. [17] modified this method. They performed it as a highly

**Scheme 1** NMR spectra data for NH-1,2,3-triazoles**Scheme 2** Polarity and acidity of 1H- and 2H-1,2,3-triazoles**Scheme 3** General methods for the synthesis of 2H-1,2,3-triazoles

regioselective process catalyzed by Cu(I) and Ru(II) salts taking place under mild conditions and giving desired products with exceptionally high yields [3].

It should be stressed that in opposite to 1H-1,2,3-triazoles, there is no universal approach to obtain 2H-1,2,3-triazoles, although numerous synthetic methods have been developed (Scheme 3) [1–6]. The most known one among them are: the cycloaddition of azides to acetylenes **15** (I), one-pot three-component cyclization

(II), reaction of 2*H*-1,2,3-triazoles **7** with electrophilic agents (III), the various cyclizations of hydrazones **16–18** (IV–VI), Boulton–Katritzky rearrangement of (*Z*)-3-arylhydrazones of 3-acyl-1,2,4-oxadiazoles **19** (VII), and intra- and intermolecular cyclization of diazocompounds **20** (VIII).

Currently, 2*H*-1,2,3-triazoles are being applied into various fields [18, 19] including their diverse biological activity and unique photonic properties. In that respect, the development of versatile methods for their synthesis became an important direction of triazole chemistry. In the following part of this critical review, we will describe the current state of the art of synthetic approaches listed above in Scheme 3.

2 Thermal 1,3-Dipolar Cycloaddition of Azides to Alkynes

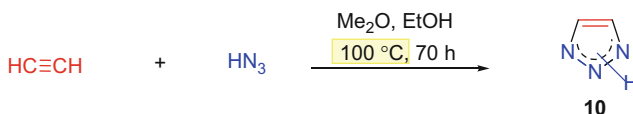
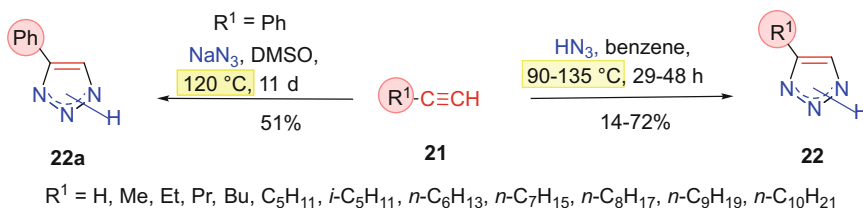
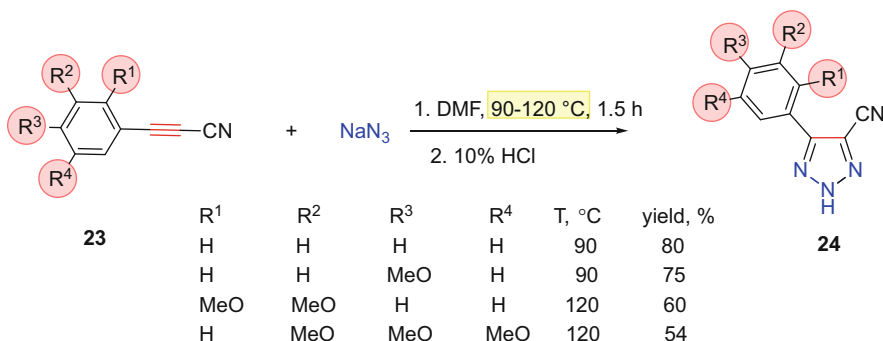
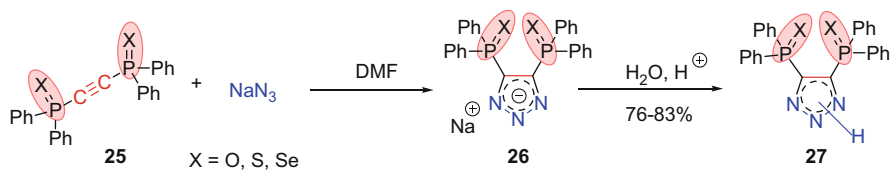
2.1 Cycloaddition of Alkynes to Hydrazoic Acid and Sodium Azide

Dimroth and Fester were first to propose the direct construction of unsubstituted NH-1,2,3-triazole ring by the interaction of hydrogen azide with acetylene [20]. The reaction was carried out by prolonged heating in a sealed tube (Scheme 4). The analogous transformation of phenyl azide with acetylene proceeded faster, in 40 h.

The dipolarophilic substrates used in 1,3-dipolar cycloaddition with azides were acetylenes bearing alkyl [21], aryl [22–27], heterocyclic [28–34], carboxy, formyl, cyano, nitro, phosphonyl, benzoyl [26, 35–44] substituents, and nucleoside residues [45]. Although the cycloaddition of alkynes to azides was characterized by a substantial exothermic effect, its high activation barrier implies that the reaction should be performed at increased temperatures. A general procedure is to heat the reactants at reflux in toluene, benzene, or alcohols, or to heat them in DMF/DMSO. For example, monoalkyl- or monophenylacetylenes **21** can interact with azides in benzene in closed vessels or after heating in DMSO [21, 22, 25] (Scheme 5).

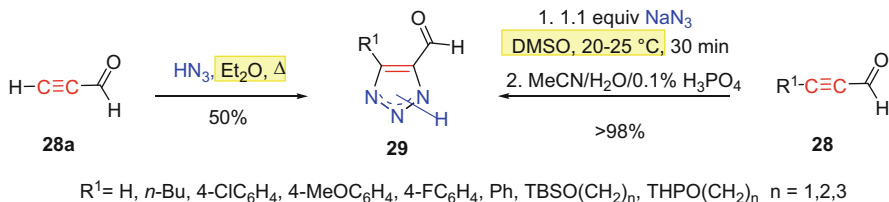
A disadvantage of this protocol is that higher temperatures shift the thermodynamic equilibrium toward the side products and the yield of the desired product can be decreased [38]. The efficiency of the process strongly depends on spatial and electronic factors of the substituents on the alkyne. It was established that introduction of electron-withdrawing groups (EWGs) enhanced the 1,2,3-triazole yields. Conversely increasing the electron-donating properties of the substituent or the presence of several electron-donating groups (EDGs) at the same time on phenylpropionitriles **23** led to decreased yields of triazoles **24** down to 54–60% even though a high temperature was employed (Scheme 6) [38].

Ethyne-bisdiphenylphosphine oxide and sulfide **25** reacted exothermally with NaN_3 in methanol to produce the sodium 1,2,3-triazolide salt **26** ($\text{X}=\text{O}$, S) (Scheme 7) [40–42]. It should be noted that the reaction with ethyne-bisdiphenylphosphine selenide **25** ($\text{X}=\text{Se}$) required longer heating. The reactivity of ethynes in this reaction decreases in the series: $-\text{PPh}_2=\text{O}>-\text{PPh}_2=\text{S}>-\text{PPh}_2=\text{Se}$

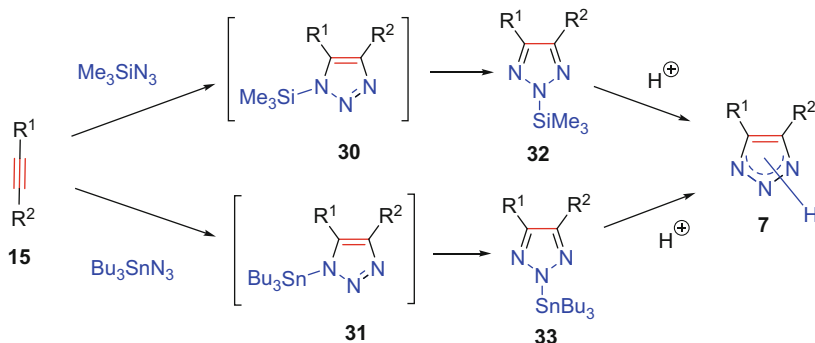
**Scheme 4** The first example of the reaction of 1,3-dipolar cycloaddition acetylene to hydrazoic acid**Scheme 5** Reaction of 4-alkyl(phenyl) acetylenes **21** with hydrazoic acids and sodium azide**Scheme 6** Electronic substituent effect on the cycloaddition phenylpropionitriles **23** to sodium azide**Scheme 7** Reaction of ethyne-bisdiphenylphosphine oxide, sulfide, and selenide **25** with sodium azide

and, consequently, the activity of the triple bond decreased in the same order. Acidification of 1,2,3-triazolides **26** yielded free acid **27** (Scheme 7).

The choice of a solvent is a crucial point for the cycloaddition reaction. Sodium azide reacted with propiolic aldehyde **28a** or its derivatives **28** in DMSO at room temperature and 4-formyl-1,2,3-triazoles **29** were obtained in quantitative yields.



Scheme 8 Synthetic routines to 2H-1,2,3-triazole-4-carbaldehydes



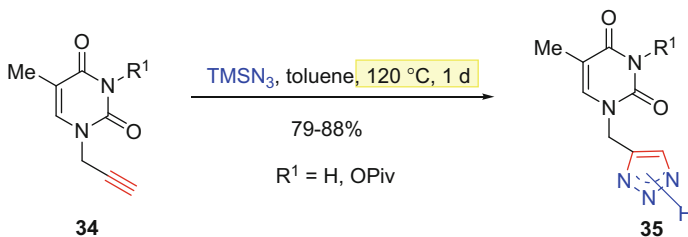
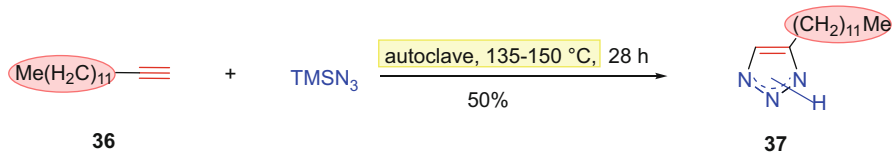
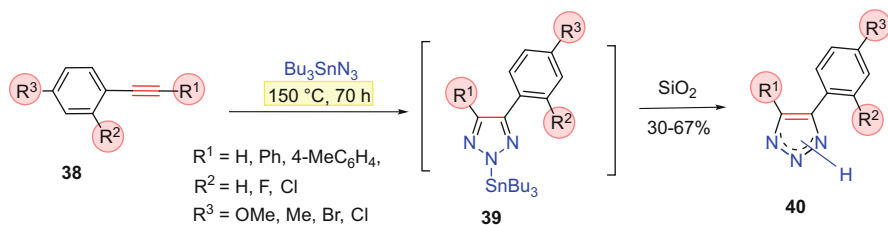
Scheme 9 1,3-Dipolar cycloaddition of alkynes with trimethylsilyl-/tri-*n*-butylstannyl azides

Only moderate yields were obtained by reflux of the same components in ether (Scheme 8) [35–37].

2.2 Cycloaddition of Alkynes to Azidotrimethylsilane and Azidotributylstannane

Further methodological development for the synthesis of 2H-1,2,3-triazoles via [3+2]-cycloaddition involved the use of trimethylsilyl or tributylstannyl azides as 1,3-dipoles (Scheme 9) [15, 22, 31, 34, 43, 46–58]. Thus, NH-1,2,3-triazoles **7** were obtained via rearrangement followed by hydrolysis of initially formed 1-trimethylsilyl- or 1-tri-*n*-butylstannyl-1,2,3-triazoles **30** and **31** (Scheme 9) in good yields.

Unlike hydrazoic acid, these azides were thermodynamically stable. Therefore, they are very convenient and relatively safe substitutes for hydrazoic acid in many reactions with various alkynes. Nevertheless, to obtain triazoles by reaction of these stable azides with acceptable yields, a prolonged heating of substrates in different high boiling solvents (usually DMF, DMA, toluene, xylene) is required. For example, to produce thymine-substituted NH-1,2,3-triazoles **35**, 1-propargyl-thymine **34** and trimethylsilylazide were continuously heated for 1 day in toluene (Scheme 10) [50].

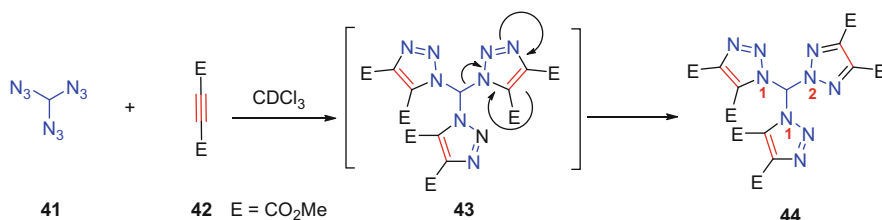
**Scheme 10** Synthesis of NH-1,2,3-triazoles **35** with thymine residue**Scheme 11** Reaction of hexacos-13-yne **36** with trimethylsilylazide**Scheme 12** Synthesis of 4,5-disubstituted NH-1,2,3-triazoles **40** by reaction of alkynes with tri-*n*-butylstannylazide

In several cases not only a higher temperature but also a higher pressure was involved [34, 56, 57]. 4-Dodecyl-1,2,3-triazole **37** was obtained by heating of tetradec-1-yne **36** in neat trimethylsilylazide in autoclave (Scheme 11) [57]. Thus, this method has an expanded scope of dipolarophiles by including inactivated alkynes with electron-donating alkyl substituents (Scheme 11).

Further examples of this cycloaddition yielding 4,5-disubstituted NH-1,2,3-triazole **40** in moderate amounts (30–67%) were described [43, 54]. The reaction of tri-*n*-butylstannylazide with mono- and disubstituted alkynes was performed by heating the reaction mixture in a sealed tube (Scheme 12) [43, 54].

2.3 Cycloaddition of Alkynes to Organic Azide

2*H*-1,2,3-triazole can be obtained by the reaction of alkynes with selected organic azides, if they have a leaving group in their structure. Such groups facilitate the hydrolysis or N-N/N-C rearrangements taking place in the next step [54–56,



Scheme 13 Cycloaddition of triazidomethane **41** with DMAD followed by rearrangement

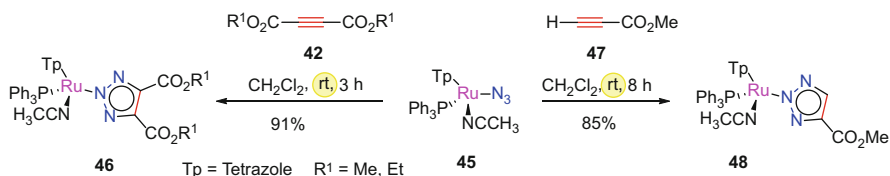
59–72]. It has been shown that 3-nitrobenzoyl, pivaloyloxymethyl, perfluoro-alkylvinyl, or trifluoromethansulfonyl azides reacted with alkynes to form NH-1,2,3-triazole [50, 54, 59–63], while (azidomethanetriyl)tribenzene, 7-azidocyclohepta-1,3,5-triene, ethyl 3-azidoacrylate, 3-azido-1,2,3-tri-*tert*-butylcycloprop-1-ene, diethyl azido(benzamido)methylphosphonate, alkyl 3-azido-2-alkenoates, and azidomethylamines produced a mixture of 2-R-1,2,3-triazole and NH-triazole, or 1- and 2-substituted 1,2,3-triazoles with an excess of the latter isomer [56, 64–71].

An interesting example of tri(1,2,3-triazole) **44** involved a step of N(1)-N(2) rearrangement occurring during the reaction of triazidomethane **41** with DMAD (Scheme 13) [71].

^1H and ^{13}C NMR spectroscopy and single-crystal X-ray diffraction experiments revealed that the 3:1 adduct exists in the structure **44** consisting of one 2-substituted and two 1-substituted triazole units. One of the three initially formed symmetrical triazole rings in **43** underwent a 1,5-sigmatropic alkyl rearrangement to yield **44**. The driving force behind this rearrangement was the demand from the molecular system to relieve the inner steric strain. Elimination of the triazole unit from the symmetrical adduct **43** followed by its re-addition led to the compound **44**.

2.4 Cycloaddition of Alkynes with Metal-Coordinated Azide Ligands

Metal-coordinated azido ligands can undergo 1,3-dipolar cycloaddition reactions. Co(III)-, Ru(IV)-, Pd(II)-, Pt(II)-, In(III)-, Ir(III)-, Mo(II)-, Os(IV)-, and Ta(V)-coordinated examples of such complexes were described [73–84]. Usually, metal-azido complexes react with alkynes to produce *Stable 2H*-1,2,3-triazolates at lower temperatures and in shorter reaction time when compared to reactions of NaN_3 and HN_3 with alkynes. It should also be mentioned that the mechanism for the reaction of metal-azide complexes with dipolarophiles is similar to the one for the reaction of TMSN_3 and BuSnN_3 described above (Scheme 9). However, the complex containing the N(1)-bound triazolate ligand immediately converts into the thermodynamically more *Stable* N(2)-bound isomer.



Scheme 14 Synthesis of complexes $(\text{CH}_3\text{CN})[\text{Ru}]\text{-N}_3\text{C}_2(\text{CO}_2\text{R})_2$ **46** and $(\text{CH}_3\text{CN})[\text{Ru}]\text{-N}_3\text{C}_2(\text{CO}_2\text{CH}_3)$ **48**

Treatment of ruthenium-coordinated azide **45** with an excess of DMAD, DEAD **42**, or methylpropiolate **47** at room temperature afforded N(2)-bound 4,5-bis(methoxycarbonyl)-1,2,3-triazolate $(\text{CH}_3\text{CN})[\text{Ru}]\text{-N}_3\text{C}_2(\text{CO}_2\text{Me})_2$ **46** and 4-(methoxycarbonyl)-1,2,3-triazolate $(\text{CH}_3\text{CN})[\text{Ru}]\text{-N}_3\text{C}_2\text{HCO}_2\text{Me}$ **48** in high isolated yields. The formation of these complexes was undoubtedly confirmed by the disappearance of the characteristic absorption band of the azide group in the IR spectra. The ^1H NMR-assigned structure for **46** was the N(2)-isomeric form, since its spectrum exhibited a singlet at δ 3.63 ppm for six protons of the methoxycarbonyl group (Scheme 14) [80].

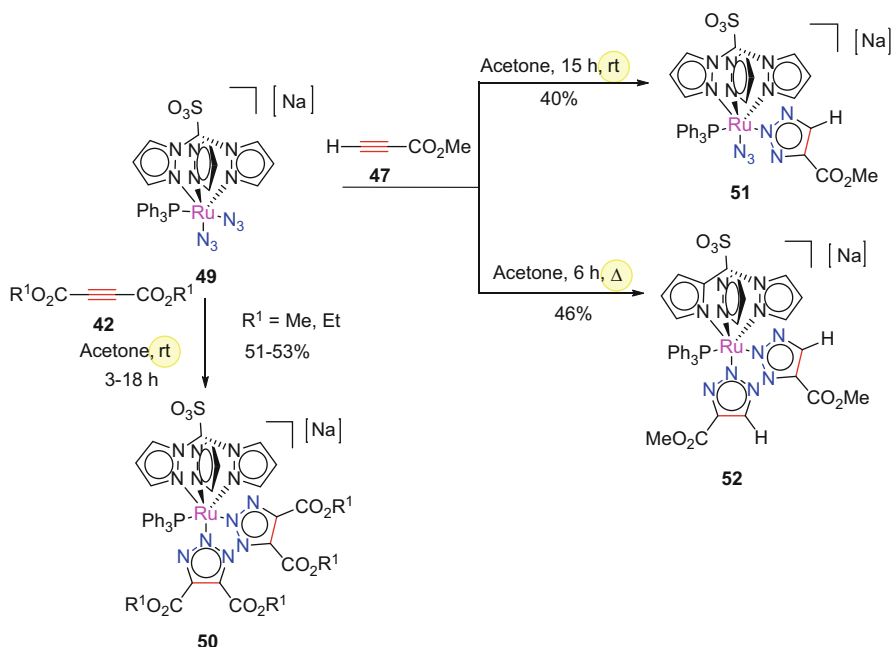
Two singlet resonances were registered at the beginning of the reaction while monitoring the reaction of azide complex **45** with DMAD, DEAD, and methylpropiolate by ^{31}P NMR spectroscopy. Those signals were attributed to the N(1)- and N(2)-isomers observed. The N(1)-isomer completely transformed into the N(2)-isomer at room temperature within $\sim 1\text{--}2$ h.

Diazido ruthenium complex **49** reacted with alkynes in a 1,3-dipolar cycloaddition fashion. Depending on the alkyne structure and reaction conditions, the cycloaddition occurred through the involvement of one or two azido groups and led to ruthenium coordinated by triazolate ligands through the N(2)-atom as in compounds **50–51** (Scheme 15) [81].

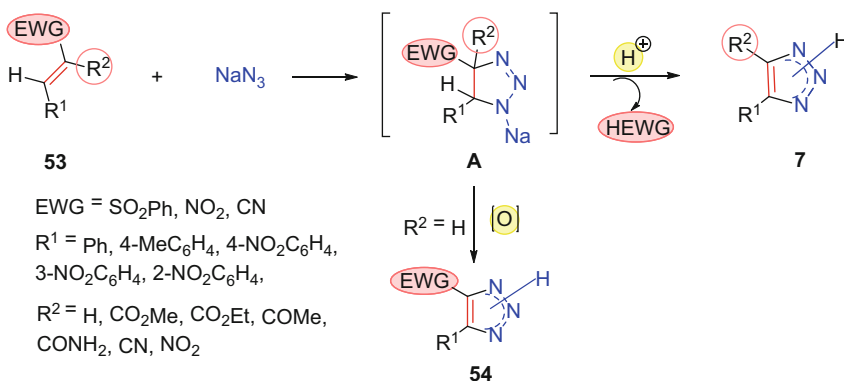
Complexes **50**, **51**, and **52** have been characterized by analytical and spectroscopic methods and X-ray diffraction crystallography.

2.5 Cycloaddition of Activated Alkenes to Azides

Other dipolarophiles that have the ability to react with azides via [3+2]-cycloaddition are activated alkenes. Their [3+2]-cycloaddition proceeds similarly to the cycloaddition of alkyne, but leads to 1,2,3-triazolines initially (**A**, Scheme 16), which was then followed by aromatization. Aromatization was achieved through the elimination of a leaving group (at the same time an EWG) or by oxidation [28, 43, 54, 85–104] (Scheme 16), resulting in two products **7** and **54**. The most convenient approach to perform this transformation was to combine cycloaddition and elimination processes, but not cycloaddition and oxidation.

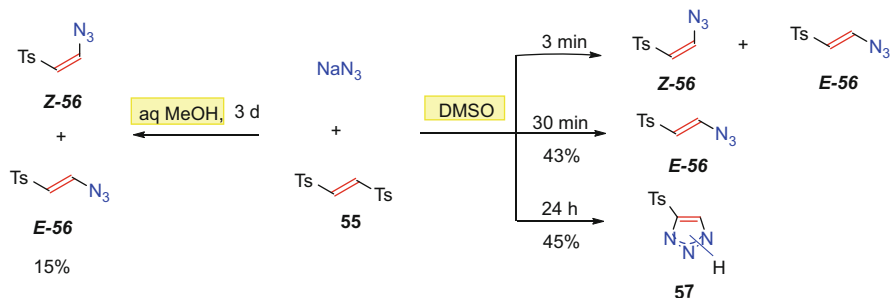
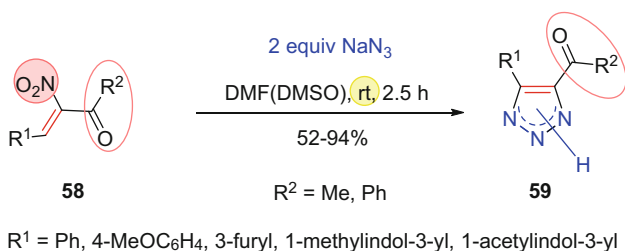


Scheme 15 Synthesis of complexes $[\text{Na}]\{\text{Ru}\{k(N^2)\text{N}_3\text{C}_2(\text{CO}_2\text{R}^1)_2\}_2\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)]$ **50**, $[\text{Na}]\{\text{Ru}(\text{N}_3)\{\text{N}_3\text{C}_2\text{H}(\text{CO}_2\text{Me})\}_2\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)]$ **51**, $[\text{Na}]\{\text{Ru}\{\text{N}_3\text{C}_2\text{H}(\text{CO}_2\text{Me})\}_2\{k^3(N,N,N)\text{-Tpms}\}(\text{PPh}_3)]$ **52**



Scheme 16 [3+2]-Cycloaddition of activated alkenes **53** to sodium azide

The yields of cycloadduct were substantially increased if the reaction of alkene with azides was carried out in aprotic solvents [86, 87]. It was observed that the reaction of sodium azide with 1,2-di-*p*-toluenesulfonylene **55** in aqueous methanol produced azidovinyl *p*-tolyl sulfone **56** as a mixture of *Z*- and *E*-isomers. On the other hand, in DMSO three products, namely *E*-**56**, *Z*-**56**, and NH-1,2,3-triazole **57**,

**Scheme 17** Reaction of 1,2-di-*p*-toluenesulfonylethene **55** with NaN_3 in different solvents**Scheme 18** Reaction of β -acetyl(benzoyl)- β -nitroethenes **58** with sodium azide

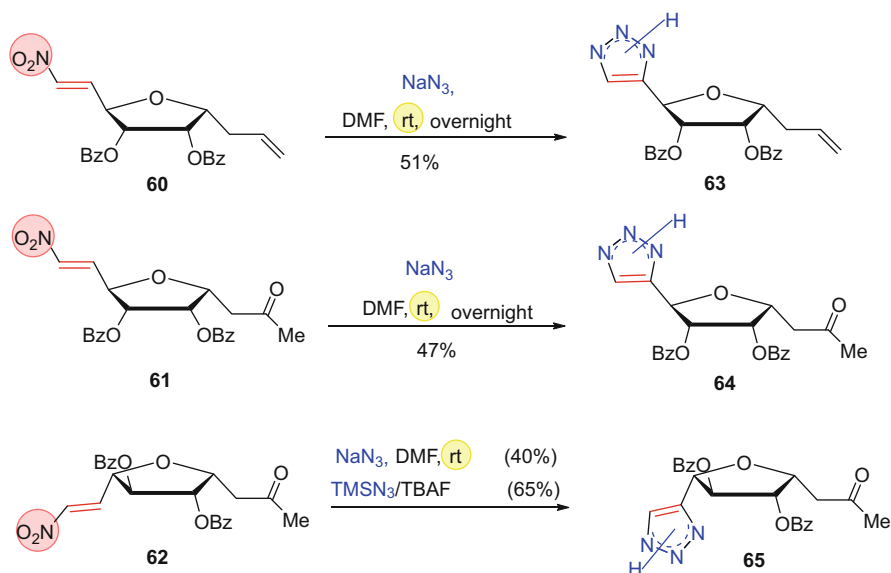
were obtained and their amounts depended on the reaction time. This observation questions the mechanism of reaction as to be simultaneous synchronic [3+2]-cycloaddition and suggests that a two-step formation for azole **57** takes place (Scheme 17).

Due to weaker reactivity of alkenes, their reactions with azides required stronger conditions. Usually, electron-deficient alkenes are utilized in order to improve the reactivity. Experimentally established elimination abilities of electron-deficient substituents on alkenes decreased in the row: benzenesulfonyl > nitro > cyano. Rare examples of halogen or thiol elimination were described as a supportive process for the transformation of 1,2,3-triazolines to 1,2,3-triazoles [99–102].

Alkenes with two geminal electron-withdrawing groups were better substrates for the [3+2]-cycloaddition with azide. The reaction of β -acetyl(benzoyl)- β -nitroethenes **58** with sodium azide proceeded in comparatively mild conditions and gave 4,5-disubstituted-NH-1,2,3-triazoles in moderate to high yields (Scheme 18) [88–92].

Activated geminal nitroethenes containing a carbonyl group as an additional electron-withdrawing unit have high synthetic accessibility and attract a lot of interest due to the ability to introduce in triazole ring biologically active fragments and different heterocycles [28, 54, 89, 91, 98, 101].

Interaction of nitroalkene-containing glycosides **60–62** with sodium azide at room temperature led to ribavirin triazole-base analogous **63–65**, obtained in



Scheme 19 Reactions of nitroalkenyl-containing glycosides **60–62** with sodium azide and trimethylsilyl azide

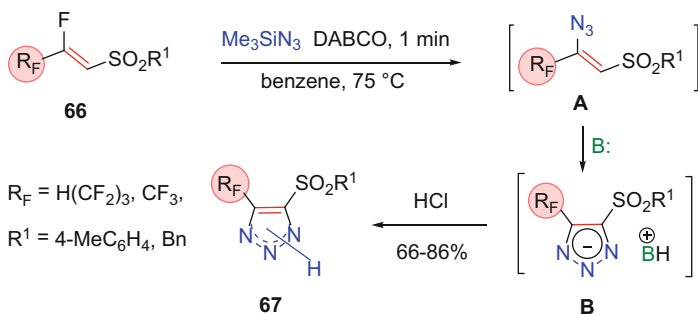
moderate yield (Scheme 19). Higher yields were achieved if the same alkene **62** reacted with TMSN_3 activated by *tert*-butyl ammonium fluoride (TBAF) added to the mixture (Scheme 19) [98].

This method was also convenient to synthesize fluorocontaining NH-1,2,3-triazoles [103–105]. The reaction of fluorinated sulfones **66** with trimethylsilyl azide in the presence of base reagent allowed to obtain 5-polyfluoroalkyl-4-arylsulfonyl-1,2,3-triazole **67** in good yields (Scheme 20) [103, 104].

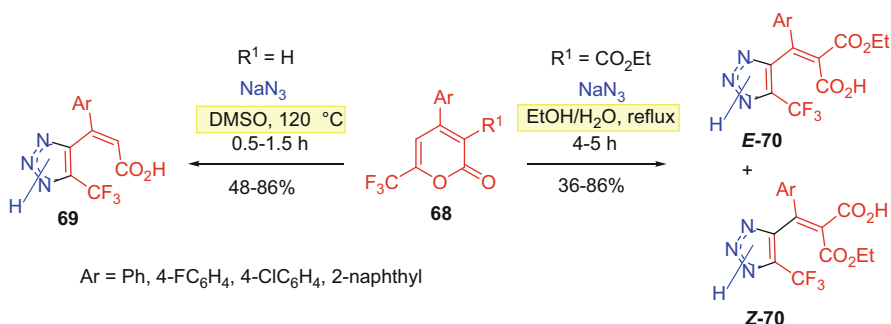
Cyclic alkenes – ethyl 4-aryl-6-(trifluoromethyl)-2-oxo-2H-pyran-3-carboxylates **68**, reacted with NaN_3 under mild condition, likely because an additional activating EWG substituent was introduced at the pyrone ring. As a result, highly functionalized trifluoromethyl-triazoles: 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl] cinnamic acids **69** and ethyl esters 3-[5-(trifluoromethyl)-1,2,3-triazol-4-yl] arylmethylidene malonic acids **70** were isolated (Scheme 21) [105].

2.6 Cycloaddition of Enamines to Azides

Several published examples of reaction of azides with electron-rich dipolarophiles, such as enamines, have been described [106–110]. Depending on the structure of the substrates different transformations may occur with initially formed 1,2,3-triazolines. Sodium azide reacted with β -monosubstituted- α -chloroenamines **72** (generated from tertiary amides **71**) in mild conditions and, as a result, 5-methyl



Scheme 20 Reaction of 1,1-polyfluoroalkyl alkenylsulfones **66** with trimethylsilyl azide



Scheme 21 Synthesis of CF₃-triazoles **69** and **70** from pyrones **68** and NaN₃

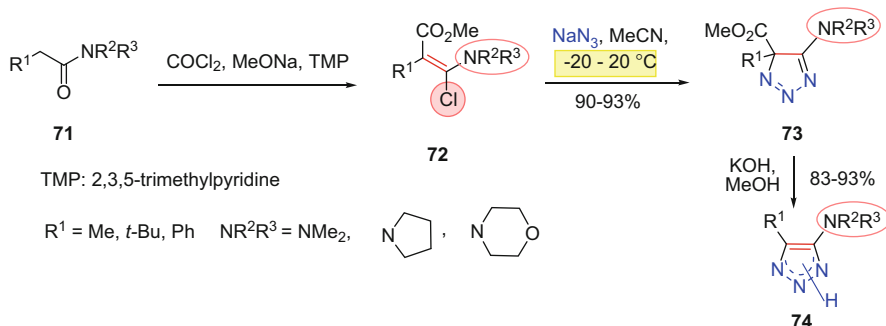
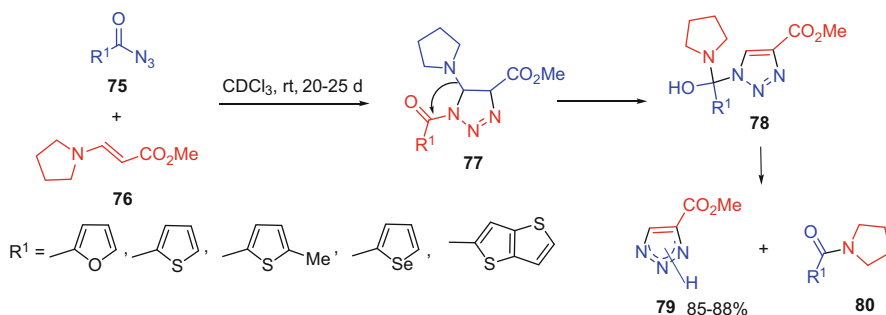
(phenyl)-2*H*-1,2,3-triazol-4-amines **74** were synthesized via 5-amino-4*H*-1,2,3-triazole-4-carboxylate intermediate **73** after saponification and decarboxylation with an excellent yield (Scheme 22) [106, 107].

1,3-Dipolar cycloaddition of heteroaroyl azides **75** to methyl 3-pyrrolidinoacrylate **76** occurred smoothly to produce 1,2,3-triazole **79** by the displacement of the pyrrolidine moiety from the 1,2,3-triazoline ring (Scheme 23) [110].

An analogous rearrangement-elimination sequence was observed in the reaction of tosyl azide with nitro- and sulfonyl enamines [108, 109].

2.7 Cycloaddition of Alkenes to Metal Azides

As it was mentioned above, the reaction of hydrazoic acid and azide ions with alkenes yields a linear product in the first place existing in dynamic equilibrium with 1,2,3-triazoline cyclic intermediates that may be transformed in several ways affording various by-products. However, when α,β -unsaturated aminoketone **81** reacted with diethylaluminium azide, obtained from diethylaluminium chloride and sodium azide in situ, no linear adduct was detected [111]. Triazole yields strongly depended on the nature of substituents R¹ and R² in aminoketone **81**.

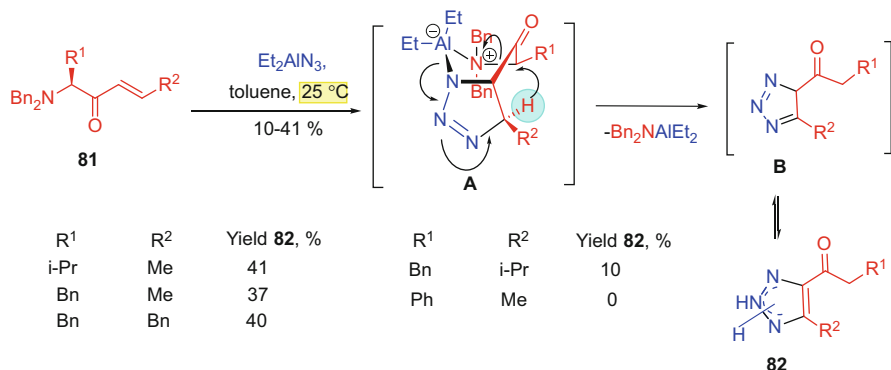
**Scheme 22** Reaction of sodium azide with β -monosubstituted- α -chloroenamines **72****Scheme 23** Reaction of azido(2-heteroaryl)methanones **75** with methyl 3-pyrrolidinoacrylate **76**

Cycloaddition of alkenes **81**, containing electron-withdrawing groups proceeded via the intermediate **A** where two rings were optimally aligned for intramolecular migration of a hydride from the triazoline C(4) atom to the α -carbon atom with a displacement of *N,N*-dibenzylamino group, activated by complexation with aluminium (Scheme 24).

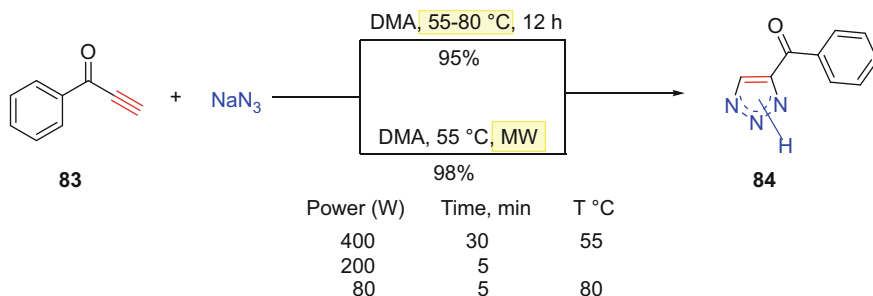
The mechanism shown in Scheme 24 was confirmed by isolation of dibenzylamine. Involvement of alkenes bearing electron-donating substituents allowed to expand the scope of the described method of synthesis of 1,2,3-triazoles via [3+2]-cycloaddition with azides.

2.8 Microwave-Assisted and One-Pot Reactions

In addition to being energy saving, the microwave irradiation also causes a striking reduction of reaction times. To surpass the efficiency of conventional protocols for cycloadditions, microwave-assisted processes were introduced in some cases [23, 51, 112, 113].



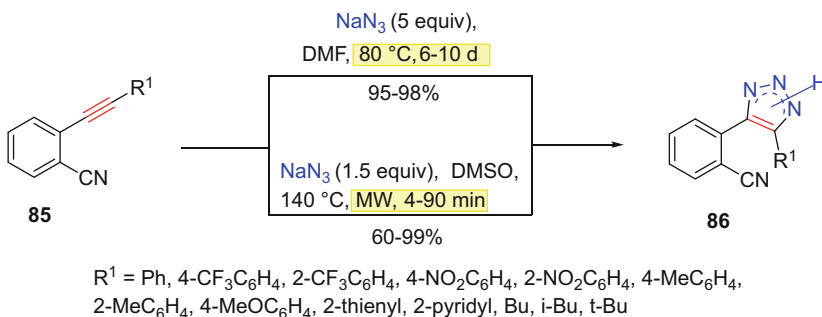
Scheme 24 Diethylaluminium azide addition to α,β -unsaturated aminoketones **81**



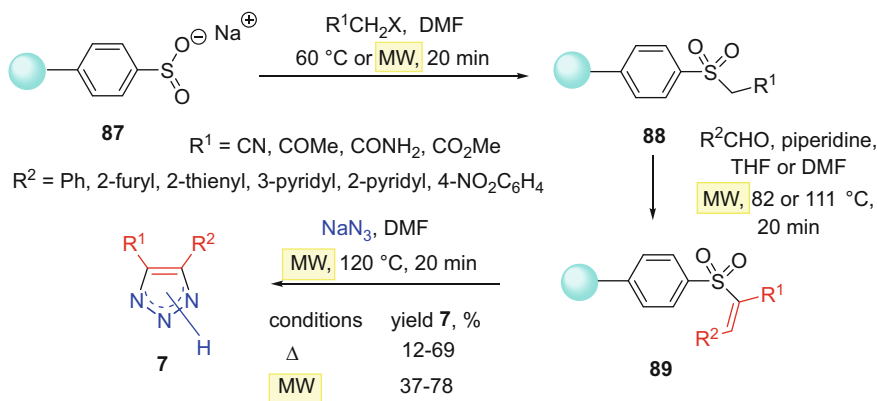
Scheme 25 Reaction of phenyl ethynyl ketone **83** with NaN_3 under conventional condition and microwave assistance

Conventional and microwave heating of the reaction of phenyl ethynyl ketone **83** with NaN_3 in anhydrous dimethylacetamide (DMA) were performed. It was shown that the procedure including microwave heating allowed the authors to achieve the desired compound **84** faster and in better yields compared to the conventional method (Scheme 25) [51].

Cycloaddition of internal alkynes **85** to an excess of sodium azide in DMF required 6 days to be completed and, even increase of sodium azide amounts (up to 10 eq) did not accelerate it (Scheme 26). Indeed, microwave irradiation noticeably improved reaction rates. The process was finished within 10 min, and triazole adduct **86** was obtained in high yield. The reaction was completed in 4–90 min for phenyl alkynes with electron-donating groups on the aromatic ring (Scheme 26) [112].



Scheme 26 Comparative study of conventional and microwave-assisted procedures on the reaction of internal alkynes with NaN_3

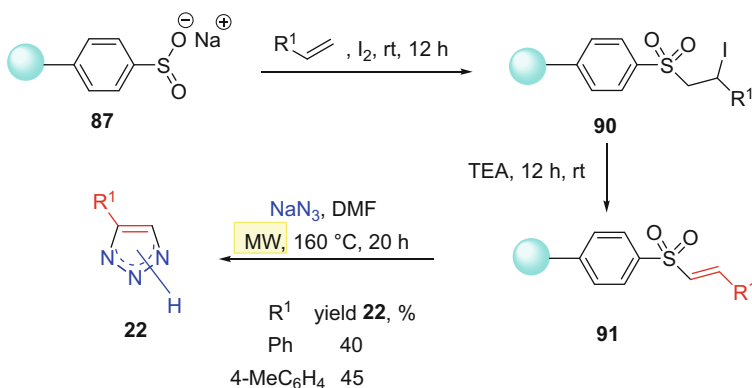
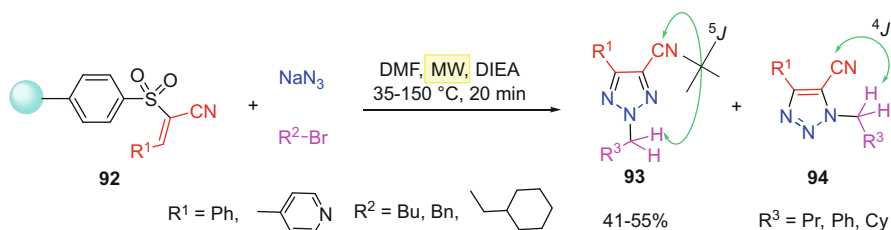


Scheme 27 Sulfonate solid-phase synthesis of 4,5-disubstituted 1,2,3-triazoles **7**

2.9 Solid-Phase Techniques for [3+2]-Cycloaddition of Azides to Alkenes

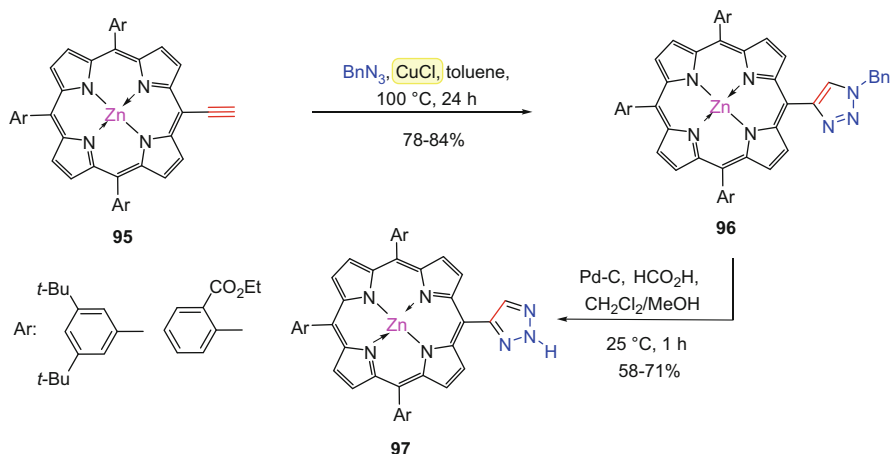
It should be mentioned that [3+2]-cycloaddition of azides to electron-deficient alkenes has received only a little attention because a poor reactivity of substrates requires applying harsh conditions. To overcome this issue solid-phase synthesis (SPS) was introduced.

A convenient solid-phase procedure for regioselective and traceless synthesis of di- and trisubstituted 1,2,3-triazoles **7** was found based on [3+2]-cycloaddition of polymer-bound vinyl sulfone to sodium azide, giving different yields (Scheme 27). Disubstituted vinyl sulfone dipolarophiles **89** were generated via Knoevenagel condensation of **88** with aldehydes. Microwave-assisted procedure in combination with solid-phase technique led to higher conversion rates and higher purity of the product **7** [113].

**Scheme 28** Sulfonate solid-phase synthesis of monosubstituted 1,2,3-triazoles **22****Scheme 29** Reaction of resin **92**, sodium azide, and alkyl bromide led to 2-alkyl-1,2,3-triazole **93**

Monosubstituted vinylsulfones **91** were obtained via ionic addition of **87** to alkenes (Scheme 28). Microwave-assisted cycloaddition of vinylsulfones **91** to sodium azide was carried out at high temperature in DMF and resulted in moderate yields of 4-aryl-1,2,3-triazoles **22** [113].

Convenient regioselective one-pot coupling procedure of resin **92** with sodium azide and alkyl halides yielding 2-alkyl-1,2,3-triazoles **93** as major isomer was described (Scheme 29) [113]. The ratio of isomers **93** and **94** in crude mixture was approximately 10:1. Their structures were confirmed by proton–carbon correlation between methylene proton and nitrile carbon in ¹³C HMBC spectra (Scheme 29). X-ray crystallography also confirmed that the major isomers were 2-substituted 1,2,3-triazoles **93**.



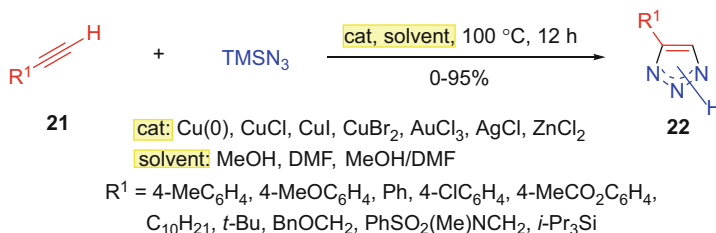
Scheme 30 Synthesis of NH-1,2,3-triazolylporphyrins **97**

3 Catalysis in Synthesis of 2H-1,2,3-Triazoles by 1,3-Dipolar Cycloaddition Reactions

Copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) offers an efficient method for synthesis of 1,4-disubstituted-1,2,3-triazoles [2–4, 6, 16, 17]. On the other hand, Ru-catalyzed reaction of terminal alkynes with alkyl azides can serve a unique routine towards 1,5-disubstituted-1,2,3-triazoles [2, 6]. In these methods the activity of inorganic azides is suppressed in mild conditions and preparation of 4,5-disubstituted NH-1,2,3-triazoles by 1,3-dipolar cycloaddition reaction is considered being useless. Conversely, there are examples of metal-catalyzed synthesis of NH-1,2,3-triazole based on sodium or lithium azide [23, 27, 114–116]. Other described examples of 1,3-dipoles for this reaction were trimethylsilyl azide [117–119] and organic azides [39, 50, 120–126]. In this case, the reaction with organic azides was followed by a rearrangement or an elimination of organic residue and lead to NH- or 2-R-1,2,3-triazoles.

Using metal salts to catalyze the reaction of organic azides with alkynes resulted in linking the NH-1,2,3-triazole moiety to porphyrinic supramolecular assemblies. *meso*-1,2,3-Triazolyl Zn(II) porphyrins **97** were synthesized via Cu(I)-catalyzed 1,3-dipolar cycloaddition of *meso*-ethynyl Zn(II) porphyrins **95** to benzyl azide [122]. The benzyl group was removed by treatment with Pd/C and formic acid (as hydrogen source) in the final step (Scheme 30).

The main problem of regioselectivity for unsymmetrical 4- or 5-monosubstituted and 4,5-disubstituted 1H-triazoles is managed by utilization of well-known ‘click chemistry’ approaches. This problem becomes insignificant in case of NH-1,2,3-triazoles and their 2-substituted derivatives due to their tautomerism or symmetry caused by the 2-substituents position. Introduction of the catalyst facilitates the cycloaddition and gives the opportunity to expand the scope of this



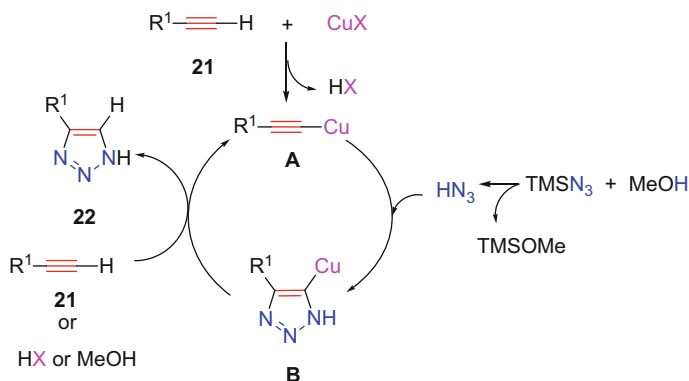
Scheme 31 Synthesis of *N*-unsubstituted 1,2,3-triazoles **22** by catalyzed [3+2]-cycloaddition reaction of nonactivated terminal alkynes **21** and TMSiN₃

reaction. This explains why metal-catalyzed syntheses currently are being very popular in triazole chemistry.

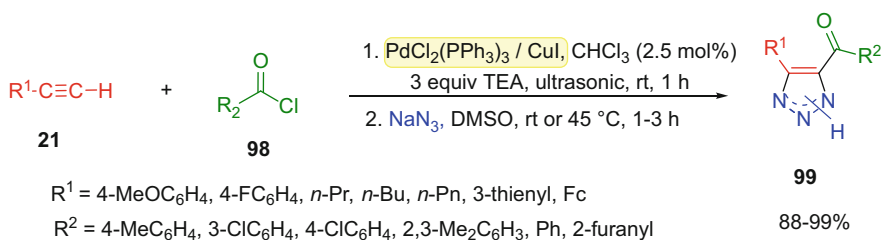
For example, the [3+2]-cycloaddition of nonactivated terminal alkynes **21** and trimethylsilyl azide proceeded smoothly in the presence of Cu(I) catalyst (CuI, CuCl, etc.) to give the corresponding NH-1,2,3-triazoles **22** in good to excellent yields (Scheme 31) [119]. Among all tested solvents, the protic ones had a larger effect on this reaction. A mixture of DMF and MeOH improved the yield of 1,2,3-triazoles **22** up to 59–69% as compared to 14–55% obtained in other cases. Other copper catalysts, such as Cu(II)Br₂ and Cu(0) powder, were also effective [119]. The reaction without a copper catalyst was characterized by a lower yield (13%). Non-copper metal catalysts (AuCl₃, AgCl and ZnCl₂) were not effective at all.

A mechanism for catalyst-activated cycloaddition, performed via multi-component one-pot synthesis technique, was proposed [115, 119, 127–131]. At the very beginning of this reaction CuX interacts with terminal alkynes **21** which result in the copper acetylide **A** [119]. Simultaneously, the formation of HN₃ occurs in situ by the reaction of TMSN₃ with MeOH. Since a C–C triple bond in a copper acetylide **A** is already activated the [3+2]-cycloaddition process immediately takes place. Protolysis of the C–Cu bond, initiated by terminal alkynes **21**, HX or MeOH occurred with intermediate **B**, affording NH-1,2,3-triazoles **22** in the final step (Scheme 32) [119].

Metal-catalyzed one-pot synthetic approaches to 1,2,3-triazoles can be classified into two types. The first one takes place as two consequent reactions of coupling and cycloaddition and leads to 4,5-disubstituted NH-1,2,3-triazoles. Sonogashira coupling reaction allows to construct acetylene dipolarophiles participating in the following step in the 1,3-dipolar cycloaddition [113, 114, 132–134]. The sequence of palladium-catalyzed Sonogashira coupling and the 1,3-dipolar cycloaddition of acyl chlorides, terminal acetylenes, and sodium azide was performed in a one-pot ultrasonic-promoted mode and led to 4,5-disubstituted-2*H*-1,2,3-triazoles **99** (Scheme 33) [132]. Reaction parameters (reaction time, yield, etc.) did not depend on the electronic properties of the substituents in the aryl terminal acetylenes and acyl chlorides. Reaction of aliphatic terminal acetylenes proceeded much slower



Scheme 32 Proposed mechanism for the formation of *N*-unsubstituted triazoles **22**



Scheme 33 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **98** through Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides, terminal acetylenes, and sodium azide

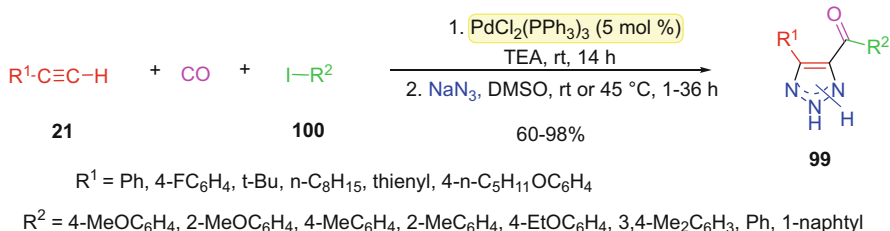
comparing to aryl acetylenes. The length of aliphatic chain was not a crucial factor affecting the yields of this process.

One-pot four-component synthesis of 4,5-disubstituted triazole **99** by Pd-catalyzed reaction of terminal acetylenes **21** with carbon monoxide, aryl iodide **100**, and sodium azide took place in mild conditions (Scheme 34) [133].

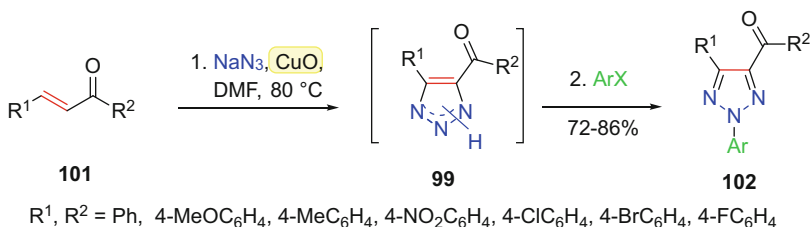
This class of one-pot reactions represents an atom economic approach, which can be easily propagated to industrial scale and is not strictly limited by the chemical diversity of substrates (Schemes 33, 34).

One-pot catalytic reactions of a second type occur when the cycloaddition is followed by nucleophilic substitution (arylation, alkylation, etc.) of the initially formed NH-triazoles, leading to 2-aryl- or 2-alkyl-1,2,3-triazoles [99, 114, 127–131]. A series of 2-aryl-1,2,3-triazoles **102** were obtained in mild conditions and with a high yield by three-component reaction proceeding via an azide-chalcone oxidative cycloaddition and post-arylation of triazoles (Scheme 35) [114]. Opting for chalcones with stronger electron-withdrawing R^1 and R^2 substituents leads to improved reaction yields.

The reaction described above was susceptible to the type of catalyst. The catalytic activity of different copper species, such as $\text{Cu}(\text{OAc})_2$, $\text{Cu}(\text{acac})_2$, CuI ,



Scheme 34 One-pot synthesis of 4,5-disubstituted 1,2,3-triazoles **99** using terminal acetylenes **21**, carbon monoxide, aryl iodides **100**, and sodium azide

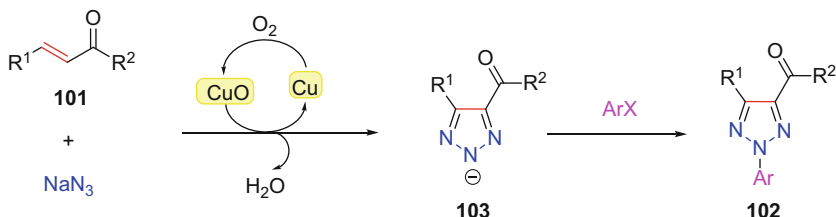


Scheme 35 Three-component reaction azide-chalcone oxidative cycloaddition and post-arylation triazole

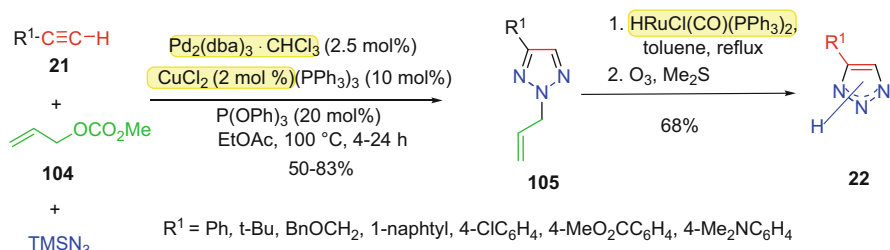
and CuO, was tested. It was found that CuO was superior and its utilization resulted in higher yields. Experimentally observed trends were in line with the proposed mechanism, involving the assumption that CuO acted not only as an oxidant for “triazoline–triazole” transformation (Scheme 16) but also as a trigger of the total catalytic process. The catalytic cycle is closed when Cu(0) is oxidized to Cu(II)O by air oxygen (Scheme 36) [114].

Regioselective formation of 2-allyl triazole **105** via three-component coupling reaction between allylmethylcarbonate **104**, TMSN₃ and alkynes in the presence of a catalytic amount of Pd₂(dba)₃ · CHCl₃ and 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 37) was reported in several publications [127–130].

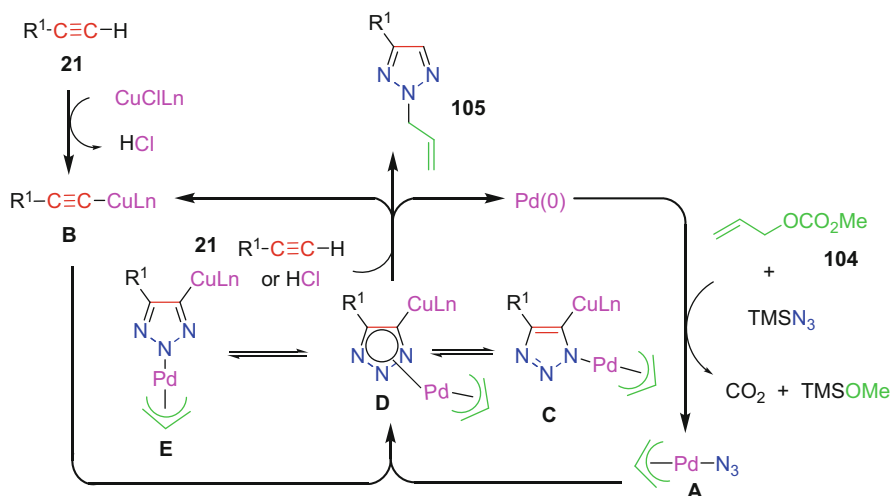
The structures of allyl triazoles **105** were determined by detailed analyses of spectroscopic data: according to ¹H and ¹³C NMR allyl triazole **105** had a symmetrical structure. The location of allyl group on the triazole ring was confirmed by NOE experiments. The mechanism for this bimetallic catalysis is shown in Scheme 38 [128]. Firstly, allylmethyl carbonate, trimethylsilyl azide, and Pd(0) reacted to yield π-allylpalladium azide complex **A**. This step of the catalytic cycle was accompanied with concomitant evolution of CO₂ and trimethylsilyl methoxide. At the same time, the copper-acetylide **B** would be formed along with the generation of HCl via the reaction of alkynes **21** and CuClLn. Then, 1,3-dipolar cycloaddition between the azide moiety of the complex **A** with copper-acetylide **B** takes place and leads to 1-(η³-allyl)(η⁵-triazoyl)palladium complex **C**. The intermediate complex **C** was suggested to exist in an equilibrium with 2-(η³-allyl)(η⁵-triazoyl)palladium complex



Scheme 36 Proposed mechanism of the catalysis of the azide-chalcone oxidative cycloaddition by the CuO

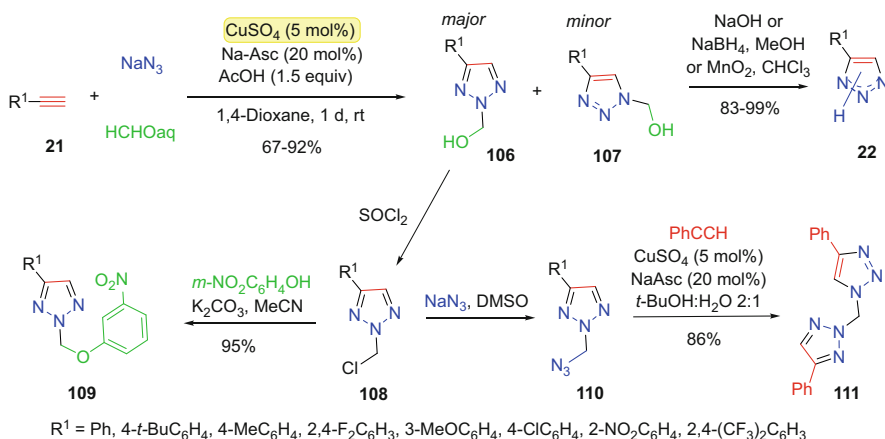


Scheme 37 Catalytic three-component coupling reaction between activated alkynes, allylmethylcarbonate, and TMSN_3



Scheme 38 Proposed mechanism for the formation of 2-allyl-1,2,3-triazoles **105** under the $\text{Pd}(0)$ - $\text{Cu}(\text{I})$ bimetallic catalyst

E through intervention of the palladium complex **D**. Regeneration of $\text{Pd}(0)$ catalyst by reductive elimination of complex **E** results in 2-allyl-1,2,3-triazole **105**. Cu would activate the $\text{C}-\text{C}$ triple bond by forming a copper-acetylide species. One of the



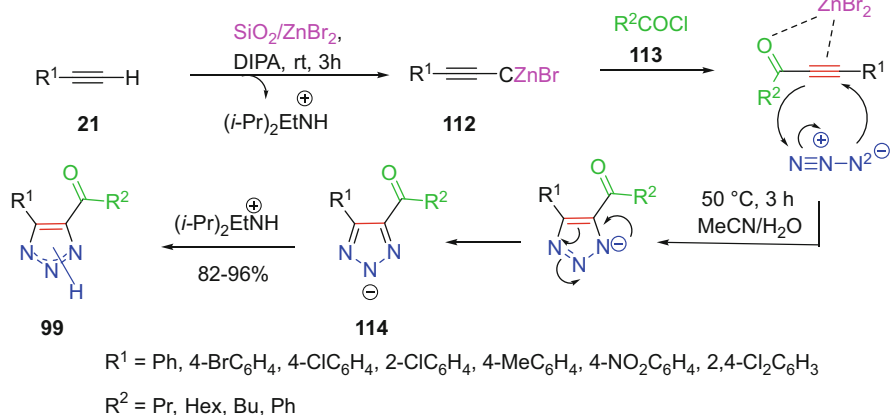
Scheme 39 One-pot two-step synthesis of *N*-hydroxymethyl-1,2,3-triazoles **106**

main particularities of this reaction was the extremely high regioselectivity since no other isomer was registered. The structure of the final product was controlled by the composition of complex catalyst.

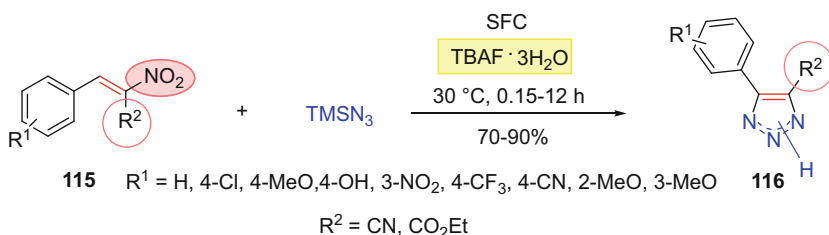
Several examples of the synthesis of 2-hydroxymethyl-2*H*-1,2,3-triazoles **106** were presented in literature [39, 131]. A one-pot stepwise reaction of formaldehyde, sodium azide, and a terminal alkyne **21** took place under slightly acidic (pH 6.5) conditions, representing another example of the synthesis of 2-substituted triazoles by catalytic cycloaddition [131] (Scheme 39).

For all tested alkynes, a mixture of 1- and 2-hydroxymethyl triazoles **106** and **107** was obtained. 2-Substituted triazoles were the major products and this fact was confirmed by the appearance of a characteristic chemical shift of the hydroxymethylene carbon atom in the ^{13}C NMR spectra and by X-ray crystallographic analysis. The identity of the minor product **107** was revealed by the heteronuclear correlation experiments. *N*-Hydroxymethyltriazoles **106** are attractive precursors due to their versatility. The described approach can be very convenient to obtain a broad variety of 2*H*-substituted 1,2,3-triazoles **109–111**, as well as NH-triazoles **22**. The authors also have evaluated the applicability of this method for gram-scale synthesis [131].

4,5-Disubstituted 1,2,3-triazoles **99** were obtained via an efficient one-pot procedure performed as a cross coupling/1,3-dipolar cycloaddition between acyl chlorides **113**, terminal alkynes **21**, and sodium azide [133, 134]. The reaction was performed in the presence of silica-supported zinc bromide (Scheme 40) [134]. When all substrates, ZnBr_2 as a catalyst and a base (DIPA or TEA) were dissolved in various solvents (MeCN, dioxane, THF, DMF) a poor yield of the desired 1,2,3-triazole **99** was obtained. However, if the reaction was performed in a sequential mode (the reaction between acyl chloride **113** and acetylene in first place and reaction with added azide afterwards) 62–96% of product was achieved. The reaction was carried out in different solvents or in solvent-free conditions (SFC),



Scheme 40 Synthesis of 4,5-disubstituted 1,2,3-triazoles **99** in the presence of silica supported-zinc bromide

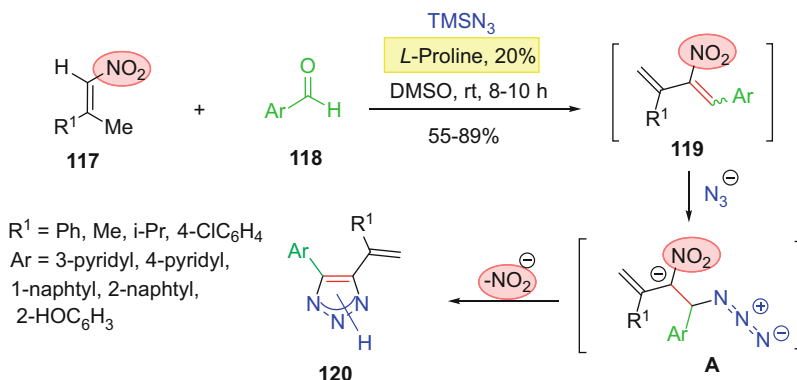


Scheme 41 Synthesis of 4-aryl-1,2,3-triazoles **116** through TBAF-catalyzed [3+2]-cycloaddition of 2-aryl-1-nitroethenes with TMSN_3 in SFC

adding ZnBr_2 or $\text{ZnBr}_2/\text{SiO}_2$ (10%) to the acyl chloride/acetylene mixture at initial step. The addition of sodium azide was postponed and 1,3-dipolar cycloaddition via ynone intermediate **112** was then yielding 2H-1,2,3-triazole **99** (Scheme 40).

A new chemically efficient, solvent-free, preparative procedure for 4,5-disubstituted NH-1,2,3-triazoles was described and proceeded as TBAF- or TBAB-catalyzed [3+2]-cycloaddition [98, 134, 135]. 2-Aryl-1-cyano- or 2-aryl-1-carboxy-1-nitroethenes **115** did not interact with TMSN_3 [98] in SFC and in an absence of any additives, even after 24 h. Addition of tetrabutylammonium bromide (TBABr) acting as catalyst allowed to obtain a triazole **116** (SFC, 30 °C). Best results were achieved if 0.1 equiv TBAF was applied. The proposed protocol was simple to perform: no dried glassware or inert atmosphere was required (Scheme 41).

Along with the metals and TBAF, TBAB, proline can catalyze the cycloaddition reaction. A convenient atom-efficient protocol for the preparation of 4,5-substituted NH-triazole **120** was developed as a one-step cascade reaction between nitroalkene,



Scheme 42 One-pot cascade synthesis of 4,5-disubstituted-(NH)-1,2,3-triazole **120**

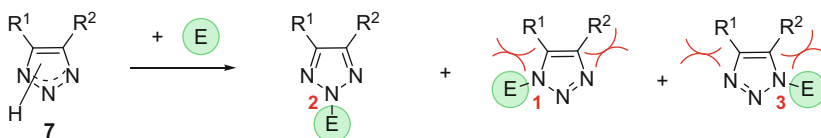
aldehyde, and NaN_3 catalyzed by proline [136, 137]. A variety of aryl aldehydes **118** and β -alkyl nitroalkenes **117** were suitable for this transformation. The reaction performance was controlled by the character of the aromatic substituent on the aldehyde and by the reaction temperature. Non-substituted and electron-deficient aromatic aldehydes worked well in this cascade transformation. The reaction with aryl aldehydes, bearing electron-donating groups, had poorer yields at room temperatures. Improved yields of 1,2,3-triazoles were achieved by increasing the temperature up to 80°C (Scheme 42) [137].

The mechanism for this reaction is shown in Scheme 42. It involves a step of in situ formation of highly reactive intermediate, 2-nitrobuta-1,3-diene **119**. Comparing to conventional procedure for 1,3-dipolar cycloaddition, the cascade approach avoids the difficulties of synthesis of α -nitroalkene dipolarophiles, and, therefore, significantly extends the scope of substrates suitable for this reaction.

The analysis of the literature on this topic has shown that a variety of diverse approaches to synthesize 2*H*-1,2,3-triazoles via a 1,3-dipolar cycloaddition of azides with alkynes/alkenes exist and includes conventional, catalytic, one-pot multi-step, and solid-phase synthetic procedures. There are obvious advantages of using them at larger scales. However, a main challenge to propagate them to industrial scales is the availability and the cost for alkynes/alkenes. In addition, the explosive character of organic/inorganic azides substantially limits their use for industrial synthesis.

4 Synthesis of 2-Substituted 1,2,3-Triazoles by Reactions of NH-1,2,3-Triazoles with Electrophiles

The vast majority of N(1) substituted 1,2,3-triazoles were obtained by the cycloaddition reaction of organic azides to alkynes and alkenes. Nonetheless, these reactions do not allow to obtain 2-substituted triazoles directly. To overcome



Scheme 43 Proposal products of the reaction of NH-triazoles with electrophilic agents

this restriction several approaches have been developed. N(2)-Substituted triazoles were synthesized by rearrangement of 1-substituted triazoles initially formed in cycloaddition of unsaturated C–C bonds to organic azides (paragraph 2.3 and 3), metal-catalyzed three-component cycloaddition (paragraph 3) metal-free solid phase synthesis (paragraph 2.9). These examples were limited to N(2)-hydroxymethyl-, N(2)-allyl, N(2)-aryl-1,2,3-triazoles (Schemes 29, 35, 36, 37, and 39).

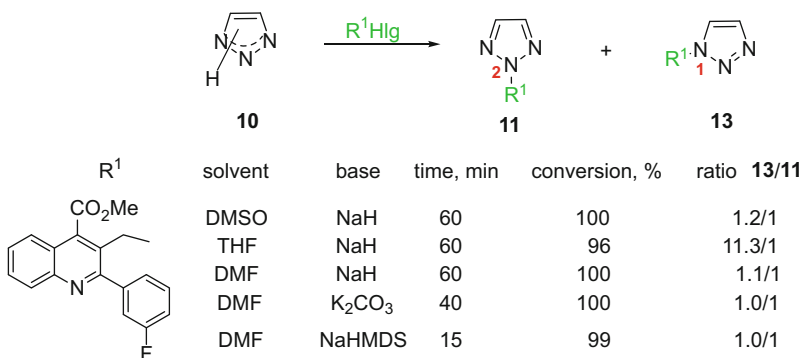
The main route to synthesize N(2)-substituted 1,2,3-triazoles is the reaction of NH-triazoles with electrophiles: alkylation, arylation, acylation, carbamoylation. Synthetic procedures for this type of reactions are well documented [1, 2, 6, 13, 18, 25, 27, 29, 31–34, 47, 49–53, 57, 59, 61, 62, 72, 83, 96, 104, 117, 118, 128, 131, 132, 136–234].

In general, all three nitrogen atoms in triazole cycle can participate in electrophilic substitution [1–6]. Most of the publications describing the transformations occurring in NH-1,2,3-triazoles pointed out that in first place a substitution at the N (1)- or N(3)-nitrogen atoms proceeds, resulting from a higher electronic density on the N(1) or N(3) atoms compared to the one at the N(2) atom (Scheme 43).

However, the thermodynamic stability of N(2)-substituted triazoles is much higher. Furthermore, the steric hindrance, caused by the presence of substituents at C(4)- and C(5)- atoms at the heterocycle, increases the predisposition for the central nitrogen atom to react with electrophiles. All listed factors can easily explain the formation of a mixture of products in the reaction of NH-1,2,3-triazoles with electrophilic agents. As a result, research for routes to increase the selectivity of the synthesis or the development of separation processes (liquid column chromatography, flash chromatography) becomes an integral part for the synthetic approach described above. Due to these reasons a selective N(2)-substitution remains a big challenge for the chemistry of triazole functionalization.

4.1 N-Alkylation of NH-1,2,3-Triazoles with Alkylhalides

N-Alkylation of NH-1,2,3-triazoles can be implemented as a nucleophilic substitution onto alkylhalides [25, 33, 50–53, 57, 61, 62, 72, 96, 118, 136, 138–171], diazoalkanes [32, 171], alkyl sulfonates or carboxylates [59, 62, 172–181], alcohols (Mitsunobu reaction) [131, 137, 182–186] or as a nucleophilic addition of alkenes and alkynes activated by EWG-groups (Michael addition) [50, 104, 187–197].



Scheme 44 N(1)/N(2)-Selectivity in the alkylation of unsubstituted NH-1,2,3 triazole **10** by alkyl halides

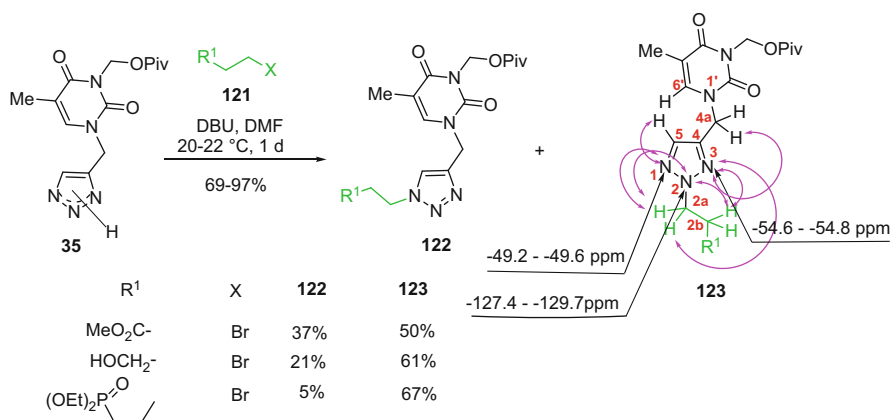
A significant drawback of this method is the formation of a mixture of regioisomeric *N*-alkyl-1,2,3-triazoles. Quite often the product ratio in this reaction is unfavorable for the N(2)-isomer, especially in the case of simple alkylating agents and unsubstituted, or monosubstituted NH-1,2,3-triazoles [149–153].

The *N*-alkylation of NH-triazoles was carried out in the usual manner in acetone, DMF, DMSO, acetonitrile, EtOH, EtOAc and in the presence of different bases (K₂CO₃, NaH, Na₂CO₃, Cs₂CO₃, EtONa, NaHMDS, LiHMDS, KHMDS, TEA, DBU) [25, 33, 50–53, 57, 61, 62, 72, 96, 117, 136, 138–171]. The application of base is necessary: the reaction was unsuccessful if the base was not added. Screening for optimal reaction conditions revealed that the choice of a solvent and a base was crucial for the kinetics and resulted in different reaction rates. However, the influence of these factors on the reaction regioselectivity is subtle. Stronger bases, such as NaH, caused the deprotonation of NH-proton and favored N(1)-substitution. On the other hand, the nature of electrophile mainly influenced the regioselectivity of the reaction [136].

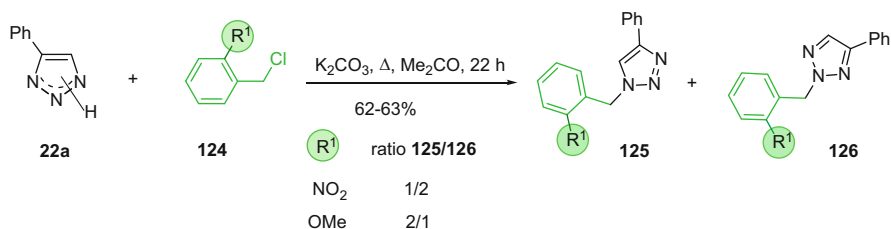
As a result, alkylation of NH-1,2,3-triazole **10** led to two isomers **11** and **13**, and their ratio depended on the electron-withdrawing nature of the substituents on the alkylation agent. The reaction was also sensitive to the type of solvent (Scheme 44) [33, 51, 118, 139–148, 157].

Variation by combination of different conditions (solvent, base and temperature) did not further improve the yield of N(2)-isomer. Despite considerable efforts being made to get a better ratio, a 1:1 mixture of 1*H*- (**13**) and 2*H*-isomers (**11**) was obtained in all circumstances.

The alkylation of C(4)-substituted triazoles may lead to different ratios of three regio-isomers, namely 1-, 2-, and 3-alkylated products, as described in several reports [25, 50, 53, 149–153]. Because of the spatial hindrance between the two neighboring groups, the thermodynamic stability of the latter isomer was decreased and some authors were able to detect this only in trace amounts and in selected cases. For example, 1-(2*H*-1,2,3-triazol-4-yl)pyrimidine-2,4-(1*H*,3*H*)-dione **35**



Scheme 45 *N*-Alkylation of 3-(pivaloyloxymethyl)-1-[(NH-1,2,3-triazol-4-yl)methyl]thymine **35**

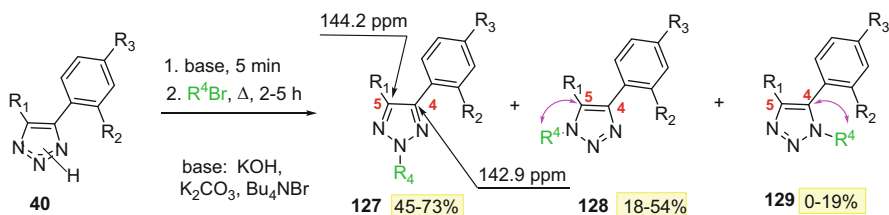


Scheme 46 Reaction of 4-phenyl-1,2,3-triazole **22a** with 2-nitro- and 2-methoxybenzyl chlorides **123**

reacted with methyl bromoacetate, 2-bromoethanol or diethyl 3-bromopropylphosphonate yielding 69–87% (combined) of **122/123** (Scheme 45) [50]. The N(2)/N(1) regioselectivity of the alkylation varied from 37:50 (methylbromoacetate) to 67:5 (diethyl 3-bromopropylphosphonate). Steric effects and the specific nature of the R-substituent on the electrophilic carbon in **121** were considered as factors to impact the course for the alkylation. The structure of 2-alkyl-2*H*-1,2,3-triazolo-nucleosides **123** was confirmed by ¹H-¹⁵N HMBC NMR spectra. The triazole nitrogen atoms were identified through their correlation with *exo*-cyclic protons of the side chain.

Alkylation of NH-1,2,3-triazole **22a** with benzyl chlorides **124** confirmed the previously established importance of electronic effects of the alkyl halide substituents R¹ for the direction of the reaction (Scheme 46) [25]: the ratio of obtained isomers **125** and **126** convincingly reflected this trend.

The problem of regioselectivity is present to the full extent for the alkylation of 4,5-disubstituted 1,2,3-triazoles [52, 53, 62, 72, 137, 154–171]. *N*-Alkylation of unsymmetrical 4,5-disubstituted-1,2,3-triazoles produced a mixture of three regioisomers: **127** N(2)-, **128** N(1)-, and **129** N(3) (Scheme 47) [52]. For this



$R^1 = H, Ph, 4-MeC_6H_4$ $R^2 = H, Cl, F$ $R^3 = OMe, Me, Cl, Br$ $R^4 = C_5H_{11}, Bn, CH_2C_6H_3Br-4, CH_2CO_2Et$

Scheme 47 Alkylation of 4,5-disubstituted-1,2,3-triazoles **40**

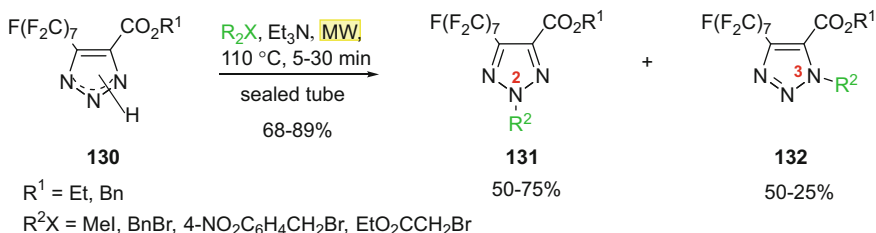
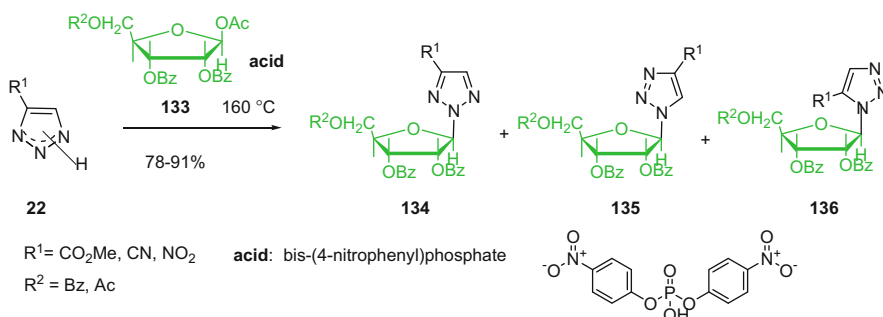
type of substrates, N(2)-isomers were the major products. N(3)-Substituted 1,2,3-triazole **129** was obtained in small proportion or could not be detected, possibly, as a consequence of steric effects.

The question of relative stability of isomers **127–129** was assessed by quantum chemical calculations. The stability of the N(1)-, N(2)-, and N(3)-isomers was evaluated at B3LYP/6-311++ G (d,p) level of theory was in line with experimentally observed ratios.

The structural assignment of compounds **127–128** was based on 2D 1H - ^{13}C NMR experiments. While no correlation was observed for **127**, the spectra of **128** and **129** exhibited different types of correlations between the H-signal of the CH_2 -group in the alkyl chain (R^4) and the C(5)- or C(4)-signals for 1,2,3-triazole ring (Scheme 47).

Alkylation of NH-triazole can be performed by a microwave procedure [62, 136, 169, 170]. A series of fluoroalkylated 1,2,3-triazoles **131** and **132** were synthesized in significant yields. Nevertheless, it should be noted that two regioisomeric triazoles were formed. As it was expected, N(2)-isomer of the 4,5-substituted triazole was the major product and the ratio between the N(2)- and N(1)-isomers depended on the spatial effects of the substituents. The structure of the isomers was carefully analyzed by 1H , ^{19}F , and ^{13}C NMR spectroscopy and X-ray diffraction [62].

It was shown that the selectivity of N(1)-alkylation of 1,2,3-triazole could be enhanced by introducing metal salts (Ag(I), Tl(III) or Hg(II)) [1]. Glycosylation of ethyl 1,2,3-triazole-4-carboxylate with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in the presence of mercuric cyanide gave N(1)-glycosylated product only [179], while acid-catalyzed fusion led to a mixture of N(1) and N(2)-triazoles [179]. The reaction of NH-1,2,3-triazole with β -bromostyrene resulted in the 2-isomer exclusively if CuI was added, in opposite to an analogous transformation described above (Scheme 48) [146].

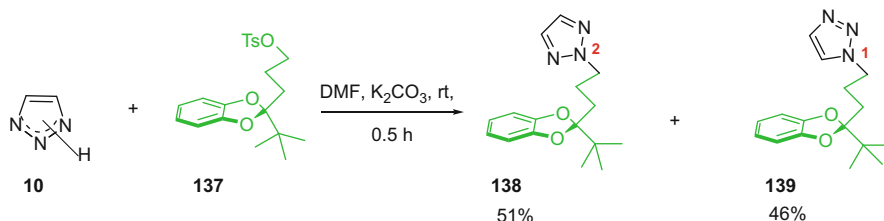
**Scheme 48** Microwave-assisted alkylation of NH-triazole **129****Scheme 49** Synthesis of 1,2,3-triazole nucleosides via procedure of acid-catalyzed fusion

4.2 Alkylation of NH-1,2,3-Triazoles with Alkyl Carboxylates and Sulf(on)ates

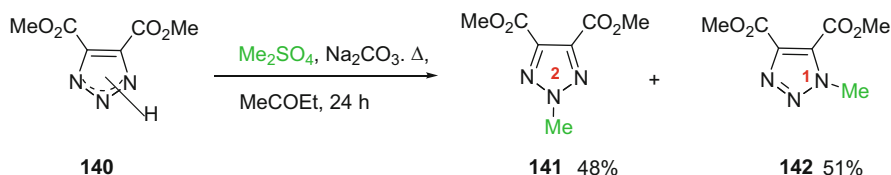
The regioselectivity factor was also very important for the alkylation of NH-1,2,3-triazoles by alkyl carboxylates and sulf(on)ates [59, 62, 172–181]. The fusion of methyl 1,2,3-triazole-4-carboxylate (**22**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**133**) in the presence of an acidic catalyst provided a mixture of nucleosides **134** and **135**, and a third isomer **136**, in approximate ratio 60:30:10 ratio (Scheme 49). 1- and 3-glycosyl-4-substituted-1,2,3-triazoles **134** and **136** were identified by comparing them with the same compounds synthesized by alternative reaction via cycloaddition of methyl propiolate with 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl azide (Scheme 49) [177–181].

Reaction of unsubstituted NH-1,2,3-triazole **10** with tosylate catechol ketal **137** at room temperature with a base led to 1,2,3-triazole isomers **138** and **139** with good yields and in equal ratio (Scheme 50) [173].

Methyl 1,2,3-triazole 4,5-dicarboxylate **140** underwent a methylation with dimethyl sulfate in methyl ethyl ketone and anhydrous sodium carbonate (Scheme 51). A mixture of the *N*-methylsubstituted isomers **141** and **142** was isolated in quantitative yield. Isomers were separated by flash-chromatography through a silica-gel column [181] and were characterized by analytical and spectroscopic analyses. The results were in accordance with known data for the isomer **142**



Scheme 50 Reaction of NH-1,2,3-triazole **10** with tosylate catechol ketal **137**



Scheme 51 Reaction of NH-1,2,3-triazole 4,5-dicarboxylate **139** with dimethyl sulfate

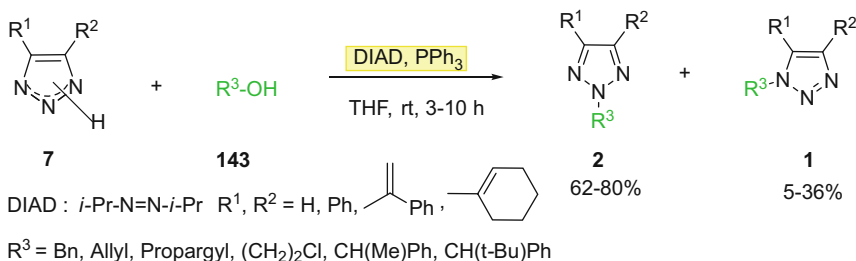
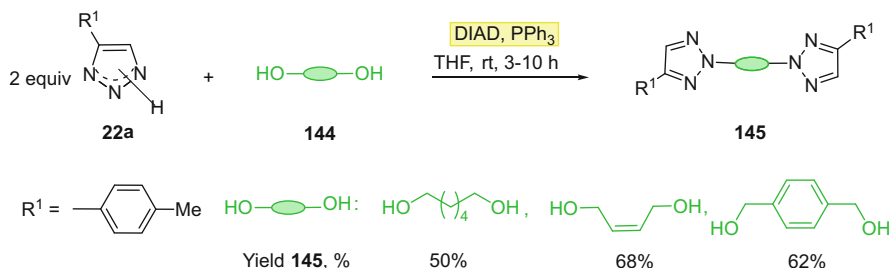
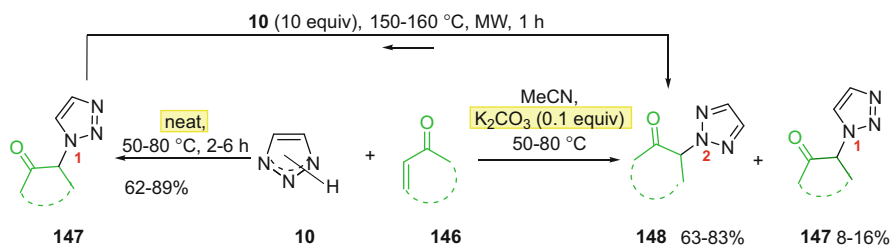
obtained from methyl azide (Scheme 51) [181]. The ratio of isomers **141/142** was 51:48, respectively, as determined by gas chromatography.

4.3 Mitsunobu Reaction of NH-1,2,3-Triazoles

The relatively high acidity (pK_a 8–10) and strong nucleophilicity make NH-1,2,3-triazoles suitable partners of alcohols reacting in Mitsunobu reaction (DIAD, PPh_3 in THF) (Scheme 52) [131, 137, 182–186].

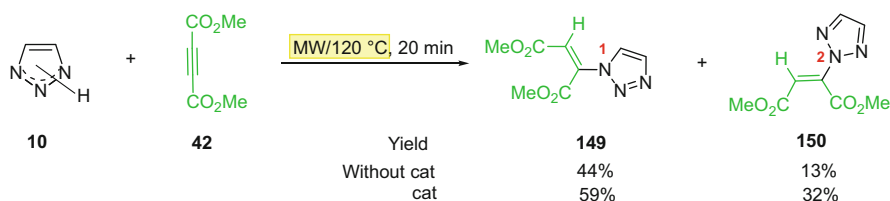
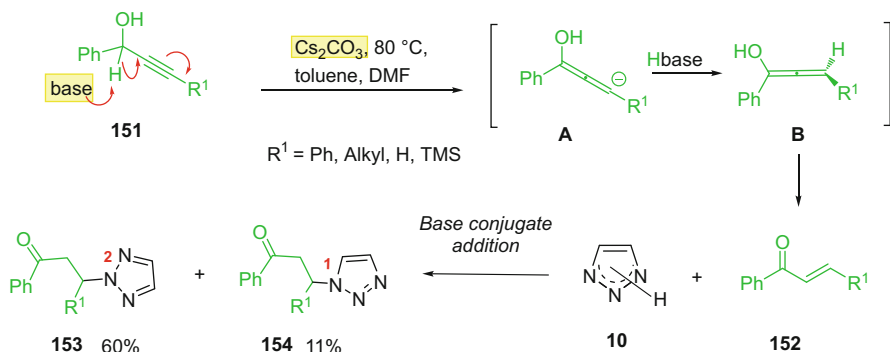
Compared to the above described examples of alkylation, significantly higher yields of N(2) products were observed for all cases of the Mitsunobu reaction. The reaction with secondary alcohols required longer times (8–12 h) and provided N(2)-isomers as the major products [184]. The significance of the choice of the alcohol for influencing the N(1)/N(2) selectivity was highlighted for the synthesis of bis-N(2)-triazole derivatives **145** (Scheme 53).

The conditions of the Mitsunobu reaction were suitable for a wide variety of alcohols and in general provided excellent yields of coupling products. Combined yields of N(1) and N(2)-isomers were more than 85%. This method can serve as a good alternative for N(2)-substitution involving no catalysts or sophisticated manipulation while altering the reactivity of the triazoles. Moreover, with the excellent stereochemical control, this method establishes the background for an asymmetric synthesis of pure 2*H*-1,2,3-triazole derivatives [184].

**Scheme 52** Mitsunobu reaction of 4,5-disubstituted NH-1,2,3-triazoles **7****Scheme 53** Synthesis of bis(1,2,3-triazoles) **145** under Mitsunobu conditions**Scheme 54** Michael addition of NH-triazole **10** to α,β -unsaturated ketones **145**

4.4 Michael Addition

Ethyl propiolate, dimethyl acetylenedicarboxylate, phenyl propiolic aldehyde, and ethylphenylpropiolate reacted with triazole salts (triazolides) giving Michael adducts, with preference for the N(2)-isomers [50, 104, 187–197]. The selectivity depended on reaction conditions. Michael addition of neat triazoles with alkynones taking place upon heating led to N(1)-triazoles **147**. However, heating of reagents in aprotic solvents (acetonitrile was the best) and under basic conditions (K₂CO₃) yielded predominantly N(2)-substituted triazoles **148** (Scheme 54) [189].

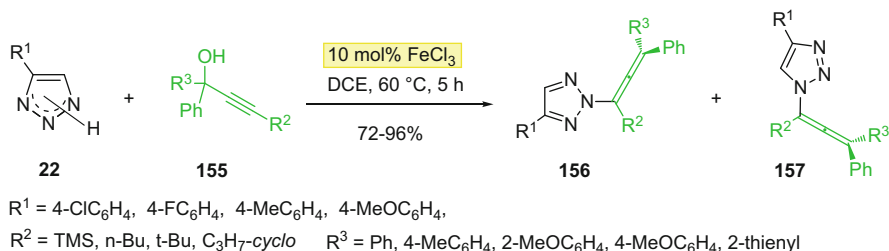
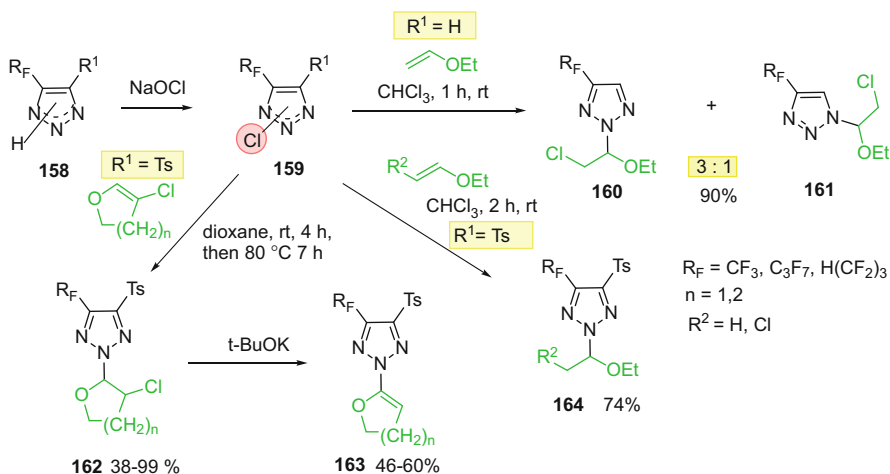
**Scheme 55** Reaction between NH-1,2,3-triazole **10** and DMAD**Scheme 56** Reaction of NH-1,2,3-triazole **10** and propargyl alcohols **150** in base condition

Michael addition of NH-1,2,3-triazole **10** and DMAD under microwave irradiation in the absence of catalyst led to a mixture of products **149** (as the *E*-stereoisomer) and **150** (as a of *Z/E* mixture in 7:3 ratio) (Scheme 55) [191]. The overall yields of **149** and **150** increased from 57 to 91% with little change in the isomers ratio when silica-bound AlCl_3 was used as the catalyst.

Conjugated addition of triazole to propargyl alcohols **151** in the presence of DBU was unsuccessful [191]. Heating of triazole **10** with propargyl alcohols **151** in toluene with DMF and DBU was sluggish. The corresponding triazoles **153** and **154** (6:1) were isolated in satisfying total yield. Redox-isomerization of accessible propargyl alcohols occurred via conjugated one-step addition of NH-azole **10** proceeded by nucleophilic attack of basic reagent. This reaction displayed a broad scope and tolerated a variety of reactive functional groups (Scheme 56) [187].

Triazole addition to tertiary propargyl alcohols occurred in a regioselective manner in the presence of iron catalyst and led to allene triazoles **156** and **157**. The reaction proceeded under mild conditions, giving a mixture of regioisomers **156** and **157** in good or excellent yields (Scheme 57) [188].

To improve further the regioselectivity of this reaction the screening of different metals ($\text{Cu}(\text{OAc})_2$, CuI , PdCl_2 , RuCl_3 , IrCl_3 , $\text{Fe}(\text{acac})_3$, LaCl_3 , CeCl_3 , $\text{Bi}(\text{OTf})_3$, AlCl_3 , SnCl_2 , LiCl) as catalyst and different solvents (MeCN, Me_2O , THF, Toluene, MeOH, MeNO_2 , DMSO, DMF, CHCl_3 , EtOAc, DCE) was performed. It was found that FeCl_3/DCE conditions were the best option [183, 188].

**Scheme 57** Reaction of 1,2,3-triazole **22** addition to tertiary propargyl alcohols **155****Scheme 58** Nucleophilic addition NH-1,2,3-triazole to electron-rich alkenes via N(2)-halogenated derivative **159**

Regioselective addition at the N(2)-position of 1,2,3-triazoles should be achieved via their transformation into N(2)-halogen derivatives. N(2)-Chlorotriazoles **159** reacted with double bonds of vinyl ethers [104], 2,3-dihydro-2H-furan (DHF), and 3,4-dihydro-2H-pyran (DHP) [197] at room temperature (Scheme 58).

Monosubstituted 1,2,3-chlorotriazole **158** ($\text{R}^1 = \text{H}$) reacted with alkenes giving a mixture of 1- and 2-alkyl derivatives **160** and **161**. At the same time, 4,5-disubstituted triazole **159** led to 2-substituted derivatives **162–164** only. Compound **163** was obtained after elimination of HCl from adduct **162**.

Obviously, due to the formation of the product mixture observed for the most cases of described alkylation examples, the separation of products becomes an important task to be performed at the final step. Luckily, the lower polarity of the desired N(2)-isomers comparing to the N(1)/N(3) ones can substantially facilitate this process.

4.5 *N*-Arylation (*N*-Heteroarylation) of *NH*-1,2,3-Triazoles

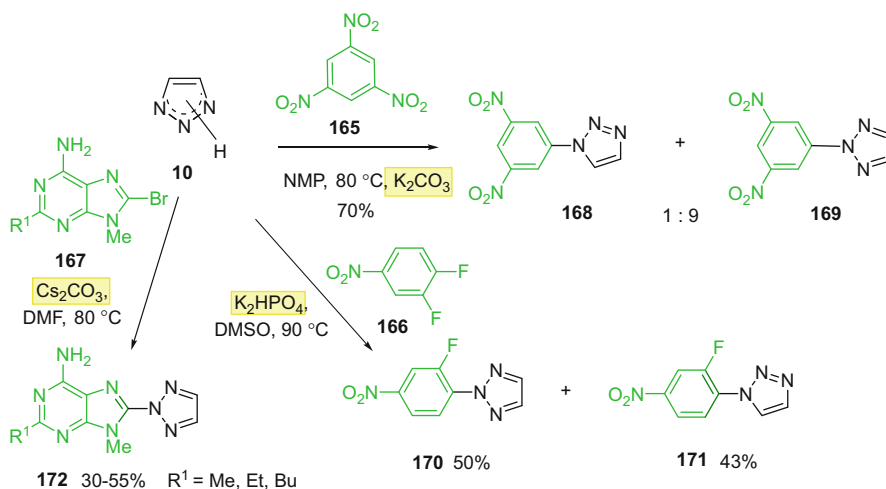
Theoretically, an ideal route to obtain *N*(2)-aryl(heteroaryl)-1,2,3-triazoles would be a direct *N*-arylation(heteroarylation) of *NH*-1,2,3-triazoles [18, 27, 29, 31, 34, 49, 117, 128, 132, 146, 149, 163, 198–223]. This reaction, occurring at higher temperatures (50–120 °C) in DMF, DMSO, MeCN, acetone, THF and catalyzed by bases (K₂CO₃, Cs₂CO₃, NaH, KOH, K₂HPO₄), could not provide an acceptable yield of desired product. It was because the reaction resulted in a mixture of two isomers in various ratios and with lower (20–50%) total yields [34, 49, 215, 217, 219]. An increase of the total yields, up to 60–70%, was observed only for *N*-arylation (heteroarylation) of *NH*-1,2,3-triazoles with activated electrophiles (1,3,5-trinitrobenzene or pentafluoropyridine) (Scheme 59) [18, 31, 132, 163, 200, 202, 210, 217, 219, 223].

To evaluate the regioselectivity for *N*-arylation/heteroarylation, the S_NAr substitution of various *NH*-1,2,3-triazoles was studied [18]. The product of arylation was stable and no C–N bond exchange occurred under the reaction conditions. This allows to evaluate directly the impact of C(4) and C(5) groups on the regioselectivity of this reaction. The introduction of phenyl group to the C(4)-atom of the 1,2,3-triazole **7** (R¹=Ph, R²=H) increased the selectivity and resulted in the major *N*(2)-arylation product, although with small ratio differences for all possible products. As reported previously, the selectivity of the reaction is controlled by both electronic and steric factors. A rise in the temperature leads to the strengthening of conformational factors and increases the steric effects of the C(4)- and C(5)-substituents. Indeed, *N*(2)-selectivity was noticeably improved with an increase of the reaction temperature (Scheme 60).

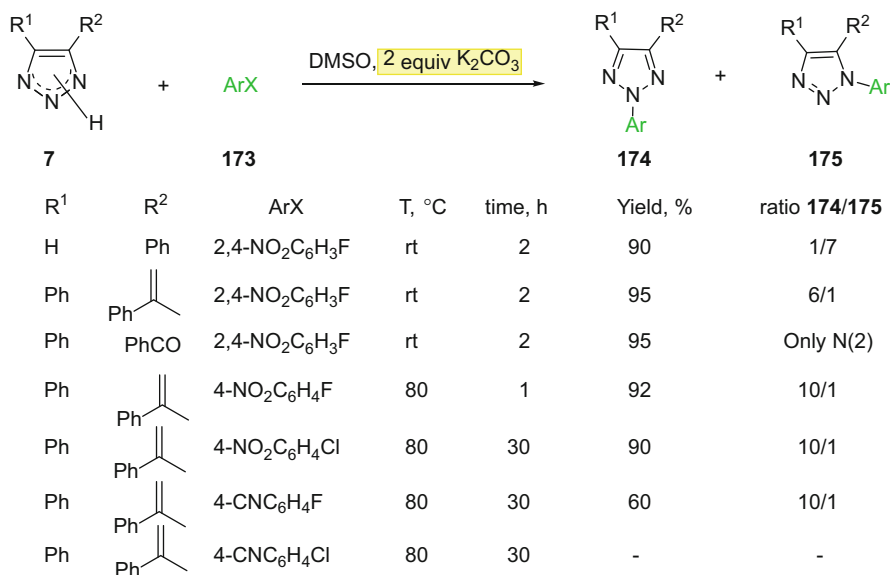
Arylation of *NH*-1,2,3-triazoles by different agents, including moderately active aryl halides was observed under Ullman conditions, e.g. in the presence of Cu(I,II) salts, and yielded *N*(2)-aryl-1,2,3-triazoles **176–178** (Scheme 61) [18, 198, 206, 221, 224–229].

The mechanism of this reaction was unresolved until now. Most likely, it involves the formation of Cu(III) intermediate followed by reductive elimination. It was established that the Cu(I) or Cu(II) oxidative addition to the carbon–halogen bond occurs via a catalytic cycle which is strongly dependable on the ligand type. Furthermore, a study of the reaction conditions established that *N*(2)-aryl-1,2,3-triazoles are formed exclusively if ligands were applied as co-catalysts. The best ligand among all co-catalysts tested (proline, glycine, Me-Gly, EDA, DMEDA, TMEDA, DACH) was proline [18].

Biarylphosphine palladium was found to be the most selective metal catalyst for the synthesis of 4,5-unsubstituted and 4-substituted *N*(2)-arylated 1,2,3-triazoles [207]. A variety of aryl bromides, chlorides, and triflates with ester, ketone, aldehyde, acetal, nitro, and cyano groups could be employed in this reaction. Slightly decreased *N*(2)-selectivity was observed for the reaction of aryl chlorides bearing an EWG at the *para*-position. For all other substrates an excellent *N*(2)-selectivity (>95%) was observed (Scheme 62).

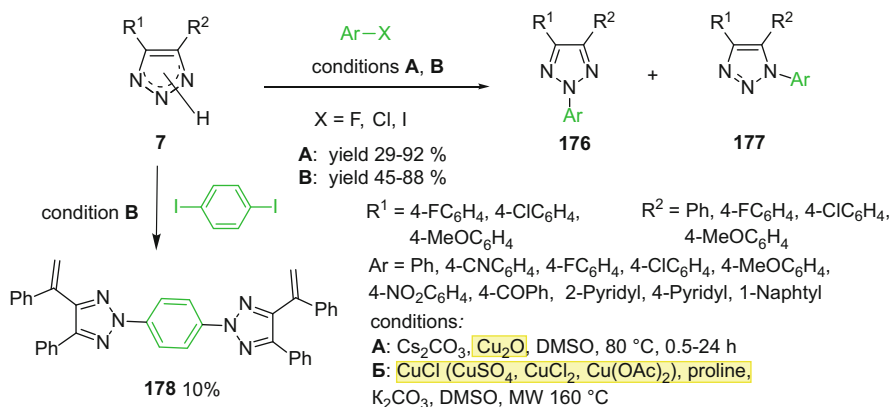
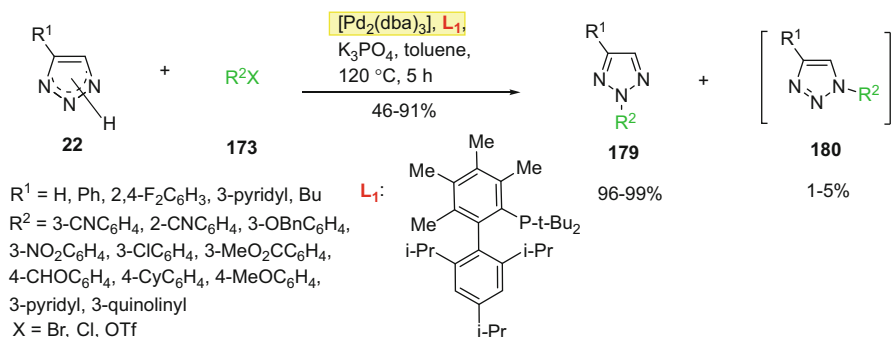
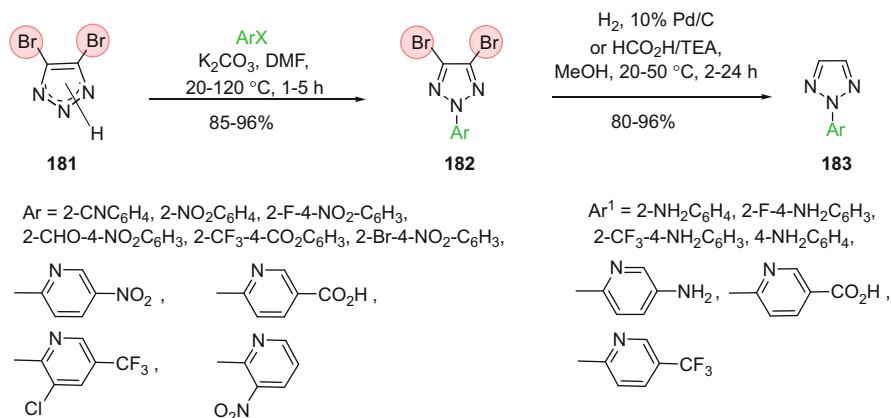


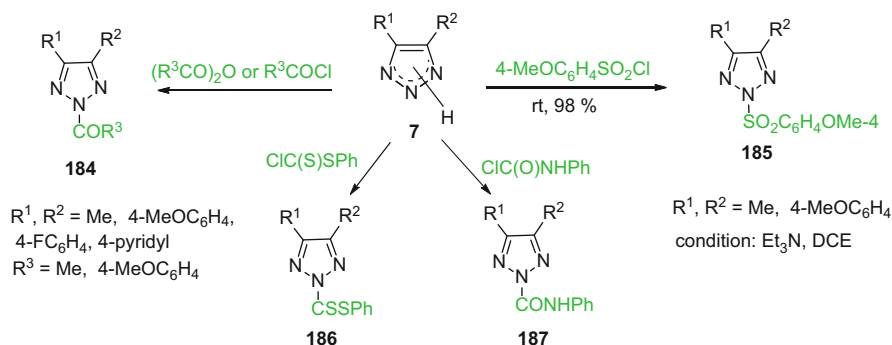
Scheme 59 Reactions of NH-1,2,3-triazole **10** with activated aryls **165**, **166** and 8-Br-purine **167**



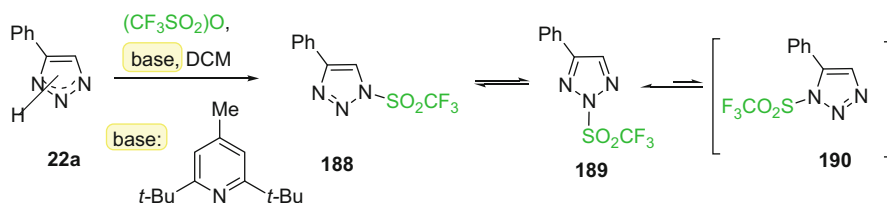
Scheme 60 4,5-Disubstituted triazole **7** arylation via S_NAr reaction

Another protocol for an efficient synthesis of N(2)-aryl-1,2,3-triazoles via highly regioselective N(2)-arylation of 4,5-dibromotriazole was executed (Scheme 63) [210]. Subsequent debromination of these triazoles via a hydrogenation efficiently furnishes 4,5-unsubstituted -2-aryltriazoles in excellent yields. Combination of steric hindrance and an electronic effects induced by 4,5-dibromo substituents

**Scheme 61** *N*-Arylation NH-1,2,3-triazole under the Ullman reaction condition**Scheme 62** N(2)-Selective arylation of 4,5-substituted and 4-substituted NH-1,2,3-triazole**Scheme 63** Selective aromatic substitution of 4,5-dibromo-2*H*-1,2,3-triazole



Scheme 64 Reaction of NH-1,2,3-triazole with acyl-, sulfonyl-, and carbamoyl chlorides



Scheme 65 Sulfonation of 4-phenyl-NH-1,2,3-triazole **22a**

contributed to the high regioselectivity observed for this reaction. Thus, the use of 4,5-dibromotriazole **181** as a nucleophile has a substantial practical value for the direct and specific N(2)-arylation of 1,2,3-triazoles.

4.6 N-Acylation, N-Sulfonation, and N-Carbamylation of NH-1,2,3-Triazoles

In contrast to *N*-alkylation and *N*-arylation, *N*-acylation, *N*-sulfonation, and *N*-carbamylation of NH-1,2,3-triazoles predominantly yielded 2-acyl-, 2-sulfonyl-, and 2-carbamoyl derivatives **184–187** (Scheme 64) [27, 29, 47, 97, 136, 185, 230–234] due to the lesser stability of N(1)-regioisomers.

2-Acyl-1,2,3-triazoles derivatives itself are relatively stable only under anhydrous and neutral conditions. The treatment of them with an acid or a base causes the hydrolysis and results in NH-1,2,3-triazoles in high yield [136, 233].

Monitoring of the sulfonation of NH-1,2,3-triazole **22a** by 1H NMR spectroscopy allowed to register previously undetected isomer **190**, formed in negligible amounts [233]. Isomers **188** and **189** were formed in approximately 1:1 ratios (Scheme 65).

Nevertheless, all attempts to isolate the corresponding *N*-triflyl triazoles were unsuccessful due to their susceptibility to hydrolysis.

The lower stability of *N*-acyl/sulfonyl derivatives of 1,2,3-triazoles limits their synthetic potential.

5 Synthesis of 2*H*-1,2,3-Triazoles by Transformations of Functionalized Hydrazones

The next major group of methods for the synthesis of 2-substituted 1,2,3-triazoles is based on transformations of hydrazones (oxidative cyclizations, Boulton–Katritzky rearrangement and various types of condensations).

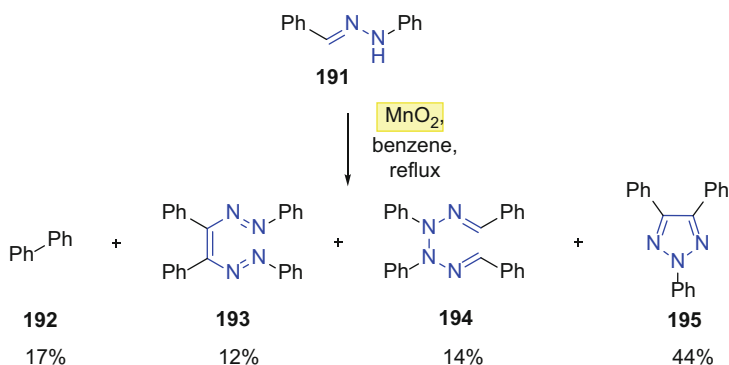
5.1 Oxidation of Mono- and Bis(arylhydrazones)

The first synthesis of a 1,2,3-triazole by the oxidation of bis(hydrazone) of 1,2-aldehydes was carried out by Pechmann [1]. Later this approach was thoroughly studied by other authors [1–6, 235–255]. Heating of ketone phenylhydrazones, bis(hydrazones), bis(arylhydrazones), or bis(semicarbazones) of 1,2-dicarbonyl compounds in the presence of MnO₂, HgO, Hg(OAc)₂, FeCl₃, NiO₂, Pb(OAc)₄ led to the formation of a mixture of products, including 1,2,3-triazole. Nevertheless, the yield of 1,2,3-triazole was quite low, 15–40%. It was shown that oxidation of arylaldehyde phenylhydrazone **191** with MnO₂ led to 1,4,5-triphenyl-1,2,3-triazole **195** mixed with by-products **192–193** (Scheme 66) [235–242].

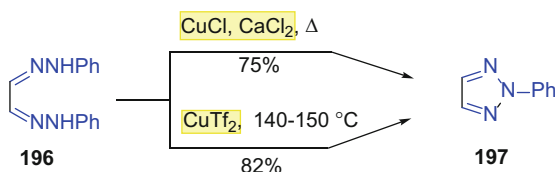
It was also found that oxidative cyclization of bis(hydrazone) **196** of glyoxal proceeded effectively in the presence of copper(I,II) salts (CuOAc, CuSO₄, CuTf₂, CuCl) (Scheme 67) [243–255].

Oxidative cyclization of bis(hydrazones) is a useful method for the two-step synthesis of triazolyl sugars. For example, D-xylose, D-ribose, D-glucose, and D-galactose were converted into phenylosazones in the first step. The latter underwent an oxidative cyclization with 1% CuSO₄, yielding 43–54% of **200** (Scheme 68) [249–255].

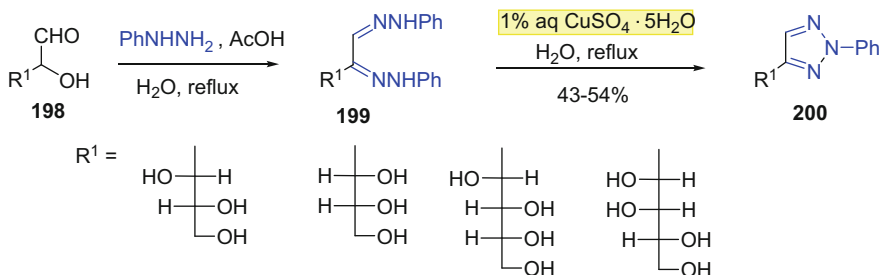
Detailed investigation on the oxidation of arylhydrazones led to the discovery of optimal conditions for the synthesis of 2,4,5-triaryl-1,2,3-triazoles and determined the mechanism of cyclization [244]. The reaction was successfully performed by heating in toluene under air with 20 mol% Cu(OAc)₂·2H₂O. In polar solvents, such as dioxane, DMSO, and THF, the yield of 2-aryl-1,2,3-triazoles **203** fluctuated from trace amounts to moderate values. The yields increased substantially when molecular oxygen was used. In contrast, the yields of target compounds **203** were reduced in a nitrogen atmosphere. The catalytic activity of different copper sources, such as Cu(OAc)₂, CuCl₂, Cu(OTf)₂, CuCl, and CuI was examined. The catalytic activity of Cu(II) salts was found to be superior to the activity of Cu(I) salts. Control experiments confirmed that no cyclization yielding compounds **203** was observed without a copper source (Scheme 69).



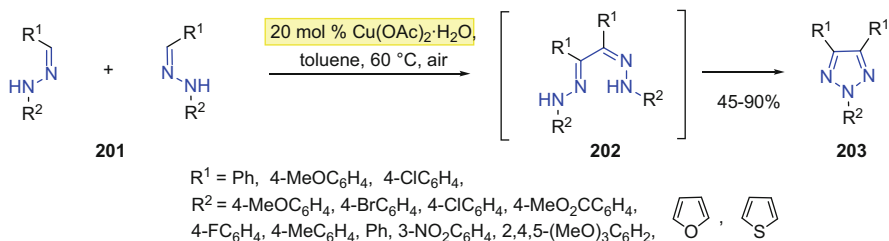
Scheme 66 Phenylhydrazone **191** oxidation in the presence of manganese(IV) oxide



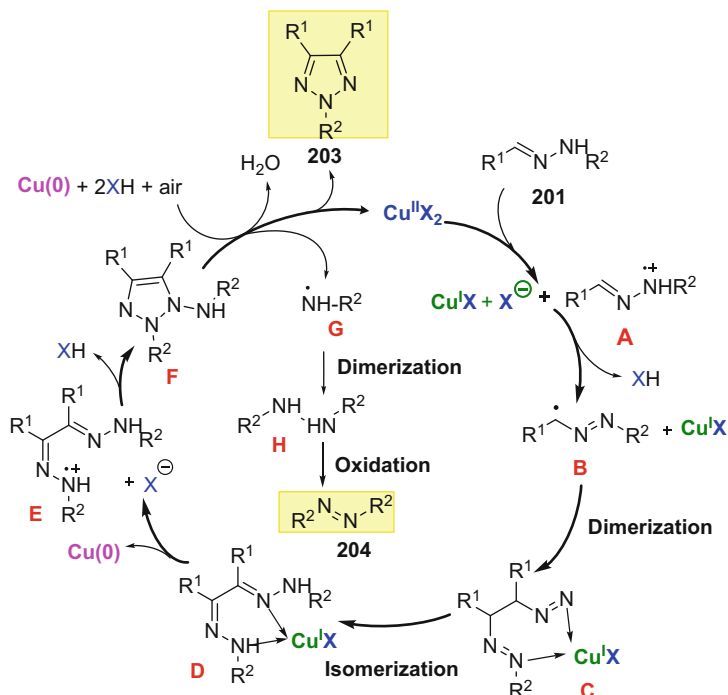
Scheme 67 Cu(I,II) salt catalyzed oxidative cyclization 1,2-bis(2-phenylhydrazono)ethane **196** to 2-phenyltriazole **197**



Scheme 68 Two-step synthesis of triazoly sugars **200**



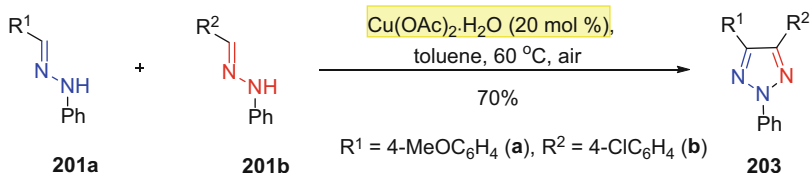
Scheme 69 Copper (II)-catalyzed synthesis of 2,4,5-triaryl-1,2,3-triazoles **201**



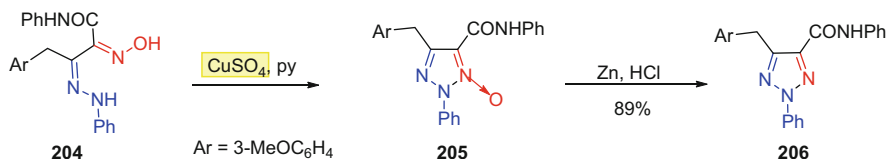
Scheme 70 Proposed catalytic cycle for the synthesis of substituted 2-aryl-1,2,3-triazoles **203** by oxidative cyclization of hydrazone **201**

It should be noted that during the oxidative cyclization of hydrazones **201** into 1,2,3-triazole **203**, intermediates **202** were isolated and their structure was confirmed by X-ray analysis. The result of the addition of TEMPO as an effective radical scavenger to the reaction mixture suggested that this transformation involved a radical intermediate. Analysis of experimental observations helped Guru and Punniyamurthy [244] to propose a plausible scheme for the synthesis of substituted 1,2,3-triazoles (Scheme 70). The generation of copper(0) was confirmed by the powder XRD analysis. Azo compounds **204** were also separated and identified by single-crystal X-ray analysis. The reaction was general, and a series of substrates underwent this cyclization to give target compounds in moderate to high yields.

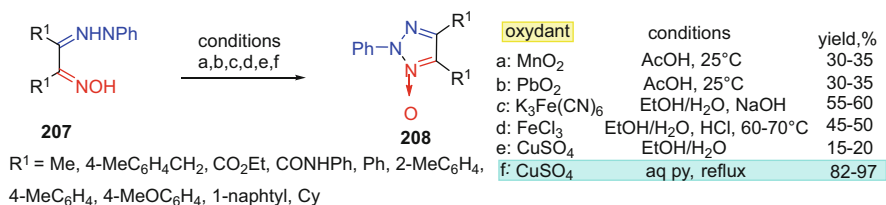
Moreover the reaction conditions were appropriate to obtain unsymmetrical 2,4,5-triaryl-1,2,3-triazoles **203** (Scheme 71) [244]. Finally, an optimal scale-up of the conditions for this reaction was developed to afford desired triazoles in 75–77% yields, but these updated conditions led to slightly extended reaction times.



Scheme 71 Copper(II)-catalyzed synthesis of unsymmetrically substituted 1,2,3-triazole **203**



Scheme 72 Synthesis of 2-phenyl-1,2,3-triazole **206** via the 2-phenyl-2H-1,2,3-triazolium 1-oxide **205**



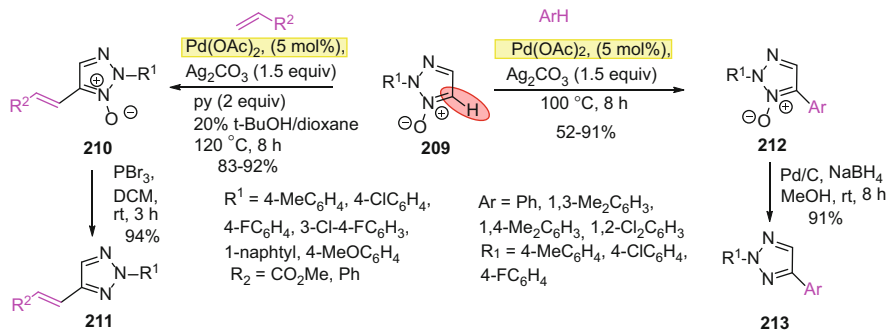
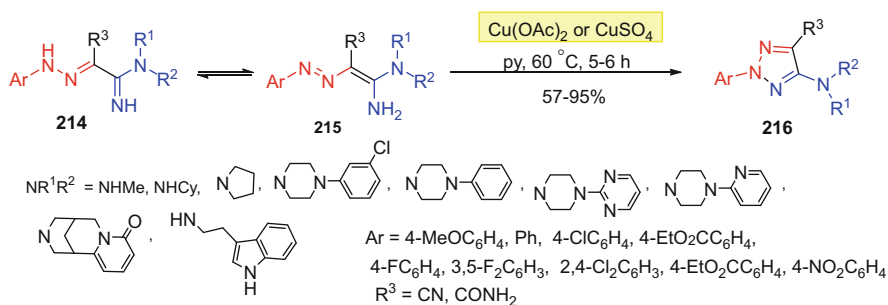
Scheme 73 The influence of various oxidative agent and solvents on the yield of 2-aryl-1,2,3-triazolium 1-oxide **208**

5.2 Oxidative Cyclization of Arylhydrazonoacetamidoximes and α -Hydrazono-Oximes

Oxidative cyclization of 2-(2-arylhydrazono)acetaldehyde led to 2-aryl-1,2,3-triazolium 1-oxides [256–268]. 1,2,3-Triazole derivatives **205** were easily transformed into 2-aryl-1,2,3-triazoles **206** by zinc reduction (Scheme 72) [259].

Various oxidative agents were applied for this reaction: $\text{K}_3\text{Fe}(\text{CN})_6$, PbO_2 , MnO_2 , FeCl_3 , CuSO_4 , and *N*-iodosuccinimide. The heating of substrates in pyridine with copper(II) sulfate was the most effective method to reach an excellent yield (82–97%) (Scheme 73) [263].

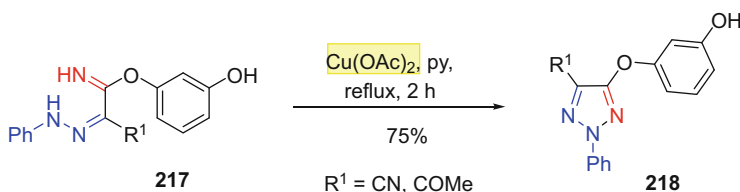
This method used to construct the 1,2,3-triazole ring has an important synthetic application. The highly selective character of C–H bond activation occurring in triazolium 1-oxides **209** allowed them to interact with alkenes (site-selective alkenylation) and inactivated arenes (cross-coupling) in a regioselective manner in the presence of a Pd-catalyst (Scheme 74) [257].

**Scheme 74** Reactions of 2-aryl-1,2,3-triazolium N-oxides **209** with alkenes and arenes**Scheme 75** Oxidative cyclization of hydrazonoacetamides **214** to 5-amino-2-aryl-2H-1,2,3-triazoles **216**

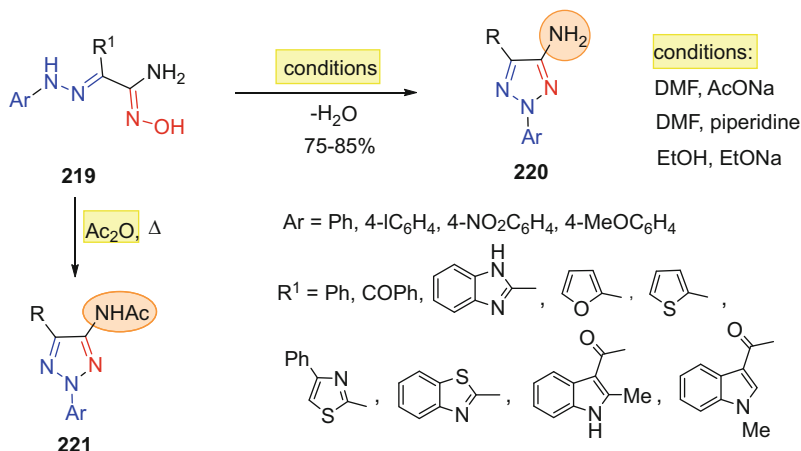
5.3 Oxidative Cyclization of Arylhydrazonoacetamides

A series of 5-amino-2-aryl-2H-1,2,3-triazoles were successfully prepared by oxidation of arylhydrazonoacetamides with copper(II) salt in pyridine [269–274]. The oxidative cyclization of 2-arylhydrazonoacetamides **214** was carried out with copper(II) acetate or sulfate in pyridine at 60°C under vigorous stirring and afforded aminotriazoles **216** in good yield (Scheme 75) [270–272, 274]. This synthetic approach allows to introduce amino, amide, and cyano groups in 1,2,3-triazoles, as well as various pharmacophores and fragments of natural products (e.g., tryptamine) and alkaloids (cytosine, piperazine) (Scheme 75).

3-Hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217** was transformed to 2-aryl-2H-1,2,3-triazoles **218** bearing an oxyphenolic group at the C(4) position by an oxidative cyclization occurring in the presence of copper(II) acetate (Scheme 76) [273].



Scheme 76 Oxidative cyclization of 3-hydroxyphenyl 2-(2-phenylhydrazono)acetimidate **217**



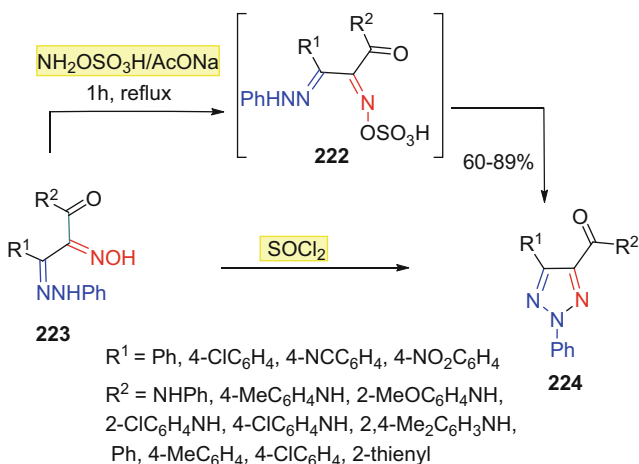
Scheme 77 Cyclization of arylhydrazonoamidoximes **219** to 5-amino- and 5-acylamino-2-aryl-2H-1,2,3-triazoles **220** and **221**

5.4 Intramolecular Cyclization of Bis(hydrazones) and Hydrazoneamidoximes

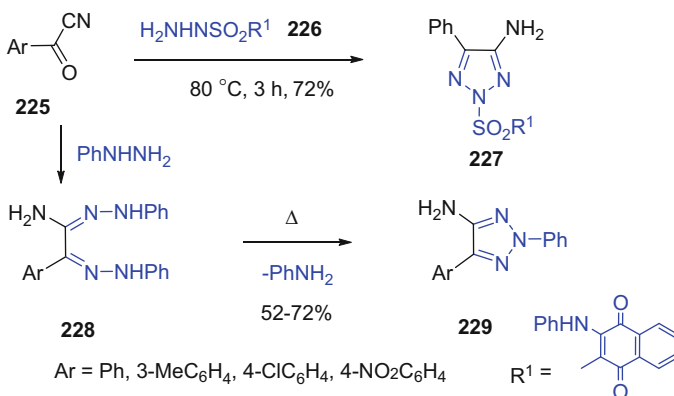
Another transformation of bis(hydrazones), hydrazoneamidoximes, and hydrazonehydrazides yielding 2-aryl-1,2,3-triazoles usually occurs under condensation conditions and is accomplished by the elimination of a leaving group [240, 275–294].

Arylhydrazonoacetamidoximes are widely accessible and can be easily transformed into 5-amino-1,2,3-triazoles by heating in DMF, EtOH with sodium acetate, EtONa, or piperidine, followed by treatment with POCl_3 , or by reflux in acetic anhydride, under microwave activation [275–281]. Refluxing hydrazones **219** with acetic anhydride causes the cyclization, which usually leads to mono- or diacetylated dehydration products (Scheme 77) [277–279].

It was shown that 1,2,3-triazole can be obtained directly from arylhydrazono-nitriles by heating them in DMF with hydroxylamine hydrochloride in the presence of sodium acetate [270].



Scheme 78 Cyclization of arylhydrazone α-oximes **222** to 2-aryl-2*H*-1,2,3-triazole-4-carboxamides **224**

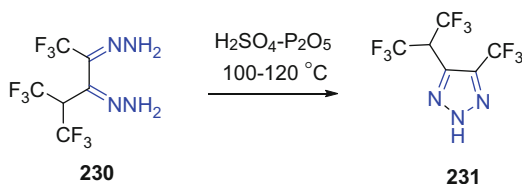


Scheme 79 Reaction of aryl nitriles **225** with the phenylhydrazine and sulfonylhydrazide **226**

Cyclization of arylhydrazone oximes **223** by dehydration agents (Ac_2O , SOCl_2 , hydroxylamine-*O*-sulfonic acid) led to 2-aryl-1,2,3-triazoles in the same manner (Scheme 78) [282–290].

Reaction of hydrazononitriles **225** with phenylhydrazine or sulfonylhydrazide **226** afforded 4-amino-1,2,3-triazoles **227** via intermediate bis(hydrazone) whose cyclization was accompanied with an elimination of aniline or sulfonamide. Bis(hydrazone) α-dicarbonyl compounds **228** were separated and identified (Scheme 79) [292–294].

Using arylhydrazone substrates with an ethoxycarbonyl group at the α-position provided a synthetic route to 5-hydroxy-2*H*-triazoles [294].



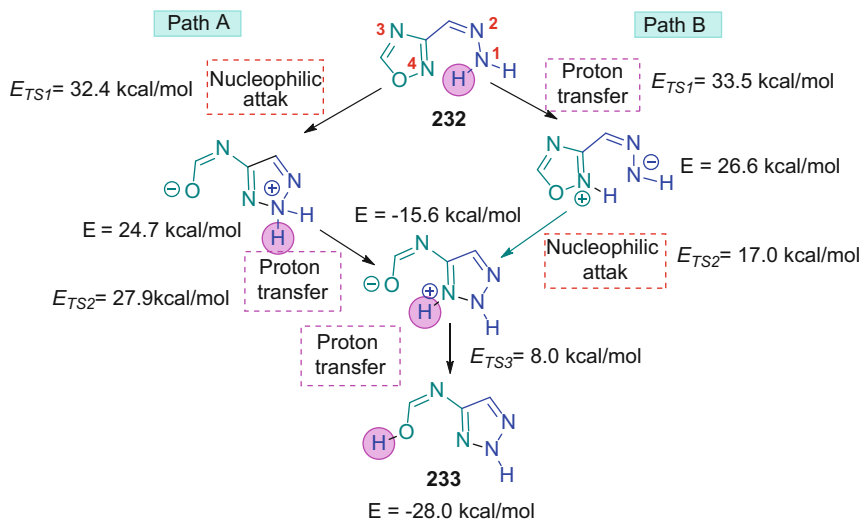
Scheme 80 Synthesis of fluorinated NH-1,2,3-triazole **231** by the cyclization of bis(hydrazono) **230**

The unsubstituted dihydrazono of α -diketone **230**, bearing two fluorinated alkyl substituents at C-hydrazono atom, underwent cyclization into (hexafluoropropan-2-yl)-5-(trifluoromethyl)-2H-1,2,3-triazole **231** by treatment with an $\text{H}_2\text{SO}_4\text{-P}_2\text{O}_5$ (3 : 1) mixture [240, 291]. It should be mentioned that α -hydrazono **230**, similarly to their nonfluorinated analogues, can be hydrolyzed exclusively into the α -ketohydrazono in the presence of concentrated H_2SO_4 (Scheme 80).

Intramolecular cyclization of bis(hydrazones) and hydrazones with the oxime groups proceeded selectively and provided novel 1,2,3-triazoles in good yield. Poor variability and availability of starting compounds (α -dicarbonyl substrates and hydrazines) limited greatly the applicability of this approach for the synthesis of new triazoles. Synthesis of 1,2,3-triazoles from bis(hydrazones) cannot be considered as an atom-economic process because aniline elimination is involved although theoretically aniline could be reconverted into phenylhydrazine. Using hydroxylamine derivatives is more useful in this case.

5.5 Boulton–Katritzky Rearrangement of 3-Hydrazono Oxadiazoles, -Furoxans and -Isoxazoles

It is well known that 1,2,4-oxadiazoles, 1,2,5-oxadiazoles (furoxans), and isoxazoles bearing a hydrazone group in the α -position of the side chain can be easily transformed into 2-aryl-1,2,3-triazoles via the Boulton–Katritzky monocyclic rearrangement [295–326]. This type of reaction represents an example of azole–azole interconversion. This peculiar case was also described as “monocyclic rearrangement of heterocycles” (MHR) recognized by Boulton and Katritzky as a general class of ring–ring rearrangements [327]. Besides its synthetic applications, this rearrangement gets a lot of attention due to the interesting aspects of its mechanism [295–304]. The process can be depicted as an internal (intramolecular) nucleophilic substitution (S_{Ni}), and therefore the reactivity of substrates can be related to the main factors affecting the reactivity towards S_{N} reactions, i.e.: (1) the nucleophilicity of the arylhydrazone α -nitrogen, (2) the electrophilic character of the N(2)-atom in the heterocycle, and (3) the strength of the N(2)/O(1) bond for the cleavage in the starting ring (1,2,4-oxadiazole, isoxazole, 1,2,5-oxadiazole) and, hence, the mobility of the O(1)-leaving group [295–304]. The last factor can be

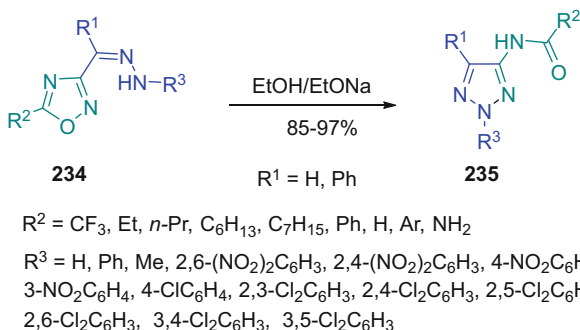


Scheme 81 Schematic representation of two pathways for intramolecular rearrangement of *Z*-hydrazone of 3-formyl-1,2,4-oxadiazole **232** to 1,2,3-triazole **233**

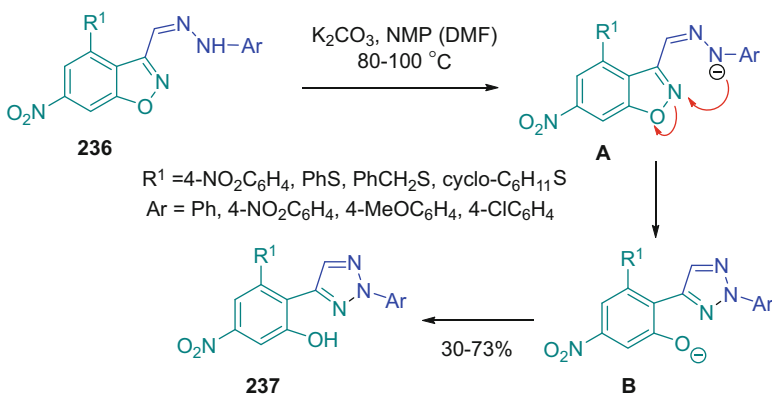
modulated by changing the type of azoles since in general the strength of N(2)–O (1) bond in general depends on the ability of the leaving group to accommodate the negative charge. It should be mentioned that the concentration of base is another crucial factor for the rearrangement process. Different pathways were confirmed to exist: a proton-concentration-independent or *uncatalyzed* pathway, and proton-concentration-dependent or *base-catalyzed* one, requiring either a general or a specific base catalyst [295–301].

Several investigations indicated the effect of the substituents on the arylhydrazone moiety on the electronic properties of the key atoms involved in the MHR, namely the hydrogen atom bound to the N(α)-atom, and the N(2) and C (5) atoms. Electron-withdrawing substituents were responsible for a decrease of reactivity of these atoms [298, 300, 304]. This S_N reaction was described in terms of push–pull shifts of electron density around the framework of broken/formed bonds. This phenomenon was accepted as an evidence for a concerted mechanism [300].

The mechanism for the uncatalyzed rearrangement of the *Z*-hydrazone of 3-formyl-1,2,4-oxadiazole was studied with DFT calculations. The study has shown that in vacuo the rearrangement occurs in a non-concerted mode along a stepwise pathway A with an activation barrier of 26.1 kcal/mol for the rate-determining step. Solvent effects (H₂O, DMSO), calculated via the COSMO continuum model, have a drastic influence on the activation barrier for the second step (this disappeared) while they slightly suppress the barrier for the first step. This suggests that under experimental conditions the reaction should proceed via an asynchronous concerted transition state where the nucleophilic attack and proton transfer occur in one kinetic step but not simultaneously (Scheme 81) [303].



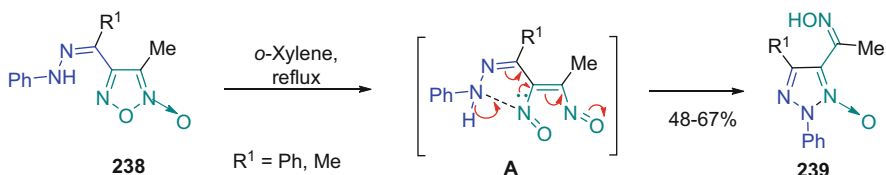
Scheme 82 Intramolecular rearrangement of the Z-aryldiazones of 1,2,4-oxadiazole **234** to 5-acylamino-2-aryl-1,2,3-triazoles **235**



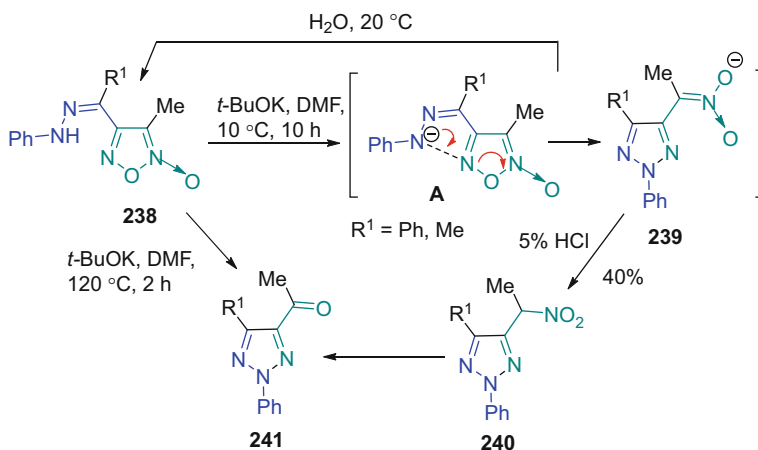
Scheme 83 Rearrangement of the hydrazone of benzo[d]isoxazole **236** to 2-aryl-2H-1,2,3-triazole **237**

Well-documented examples of this rearrangement include transformations of 1,2,4-oxadiazoles, bearing an arylhydrazone group [295–318]. They were observed at room and higher temperatures and in different solvents: dioxane/water system with buffers, in benzene and other organic solvents with various amines or activated by pyrolysis, copper catalysis, or photo- and microwave irradiation. The processes occurred faster in aprotic dipolar solvents, such as DMSO. Heating of substrates above their melting points could also trigger the rearrangement [300]. The availability of the substrates and the considerably convenient reaction conditions allowed to obtain a large series of 1,2,3-triazoles by this method (Scheme 82) [295–318].

Hydrazones of isoxazoles, benzoisoxazoles, and pyrazoloisoxazoles underwent ring-opening/recyclization when treated with K_2CO_3 in *N*-methylpyridine (NMP) or EtOH and gave 1,2,3-triazoles **237** with moderate yield (Scheme 83) [319–322].



Scheme 84 Thermally induced rearrangement of furoxanoketones phenylhydrazones **238**



Scheme 85 Base-induced rearrangement of furoxanylketone phenylhydrazones **238**

The study of rearrangements of noncondensed furoxan hydrazone derivatives **238** helped to identify two kinds of processes: rearrangement through dinitrosoethylene intermediate (1) (Scheme 84) and rearrangement resulting in 1-nitroalkylazoles (2) (Scheme 85). Reactions were initiated either thermally or by adding various bases. The thermally induced rearrangement leading to **239** was executed by refluxing a solution of furoxan phenylhydrazones in *o*-xylene [323–326].

The second variant of rearrangement for *Z*-phenylhydrazones was observed in basic conditions and at different temperatures. The best yield was achieved with a *t*-BuOK solution in DMF at 10 °C.

Rearrangement of *Z*-phenylhydrazones **238** occurred in the presence of base at different temperatures. In order to isolate the target compounds the reaction mixture was acidified in the final step. An attempt to isolate the product by slow dropwise addition of water to the reaction mixture resulted in the starting phenylhydrazones **238**. The reversible monocyclic rearrangement of the intermediate 1,2,3-triazole **239** into the corresponding furoxan was observed in aqueous alkaline media. The rearrangement of compounds **238** in the presence of *t*-BuOK at high temperature resulted in 3-acetyl-2,4-diphenyl-2*H*-1,2,3-triazoles **241** (Scheme 85). The formation

of compounds **241** may be explained by the participation of 5-(nitroethyl)-1,2,3-triazole **240** formed at the first stage in a Nef-type reaction. An insignificant amount of ketone **241** was also detected when the reaction was performed at 10°C (TLC monitoring) [323–326].

These examples of rearrangement of hydrazone derivatives were actively studied during the last decade. The attention was caused by the interest in the mechanistic details for this transformation. The main advantage for this method towards 1,2,3-triazoles consists of the possibility to introduce desired functional groups (cyano, amine, amide, ketone, etc.), while condensation of bis(hydrazones) and α -oxime hydrazones lacks this opportunity.

6 Intra- and Intermolecular Reactions of Diazocompounds

Dipolar cycloaddition of diazoalkanes **242** to nitriles **243** in the presence of base (*t*-BuOK) led to 4,5-disubstituted 2*H*-1,2,3-triazoles **7** (Scheme 86) [328–333]. In the reaction with diazomethane were obtained three regioisomers, namely **245–247**, as a result of alkylation of NH-triazoles **7**.

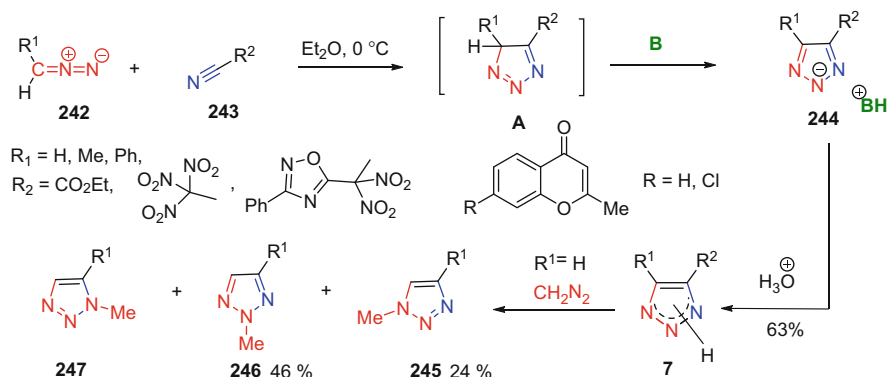
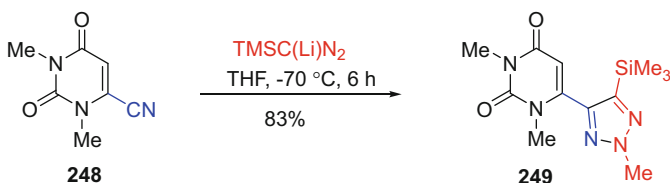
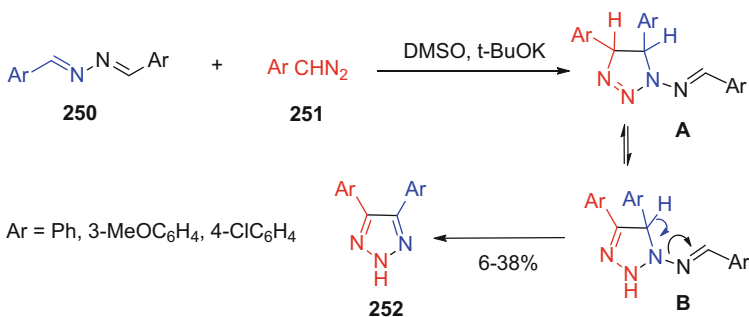
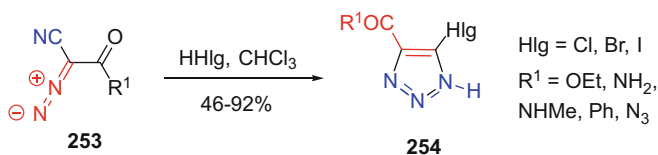
The high reactivity of exocyclic carbonitrile substituent at position 6 in uracil **248** caused it to interact with trimethylsilyldiazomethane (two equiv). Formed NH-1,2,3-triazole underwent in situ the methylation of N2 atom at the next step and derivative **249** was obtained (Scheme 87) [331].

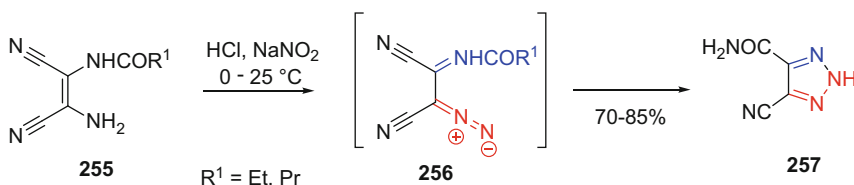
Other groups than nitriles can be involved in this type of reaction. Examples of azomethine double bonds reacting in 1,3-dipolar cycloaddition with diazomethane, yielding two or three isomers of *N*-alkylated triazoles, are also known [332, 333]. The reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl) benzene **251** led to symmetrical 4,5-diaryltriazoles **252** (Scheme 88). However, yields were significantly lower than the ones for the reaction shown in Scheme 87 [332].

The cyclization of diazo compounds containing cyano, amide, amidine, imidate groups at the α -position served as a convenient tool to obtain various derivatives of 1,2,3-triazole (Scheme 89) [334–337].

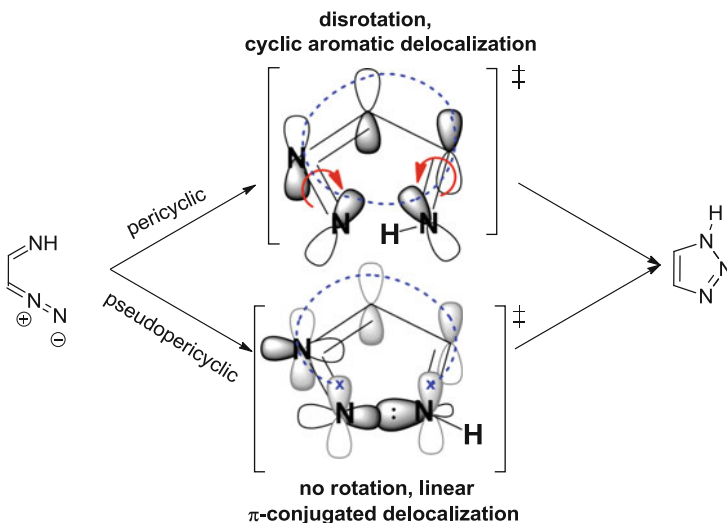
Intramolecular cyclization of diazo compounds, obtained by diazotization of *N*-(2-amino-1,2-dicyanovinyl)amides **255** in aqueous HCl, proceeded very fast and led to 5-cyano-2*H*-1,2,3-triazole-4-carboxylic acid amide **257** (Scheme 90) [334].

Besides the synthetic importance, diazo compounds are considered as attractive models to investigate the theoretical aspects of pericyclic/heteroelectrocyclic reactions frequently observed in heteroatomic π -conjugated compounds [337]. A spatial arrangement of frontier orbitals in the substrates induced them to react via symmetry-controlled pericyclic or symmetry-control-independent pseudopericyclic reactions (Scheme 91) [338]. The absence of electron–electron repulsion for the latter type of reaction substantially decreases the activation barriers and explains why this type of reaction can occur relatively easily.

**Scheme 86** Reaction of diazomethanes **242** with nitriles **243****Scheme 87** Reaction of 1,3,6-trimethyluracil **248** with $\text{TMSC}(\text{Li})\text{N}_2$ **Scheme 88** Reaction of 1,2-bis(arylmethylene)hydrazines **250** with (diazomethyl)benzene **251****Scheme 89** Intramolecular cyclization of α -diazonitriles **254**



Scheme 90 Intramolecular cyclization of N -(2-amino-1,2-dicyanovinyl)propionamide **255**



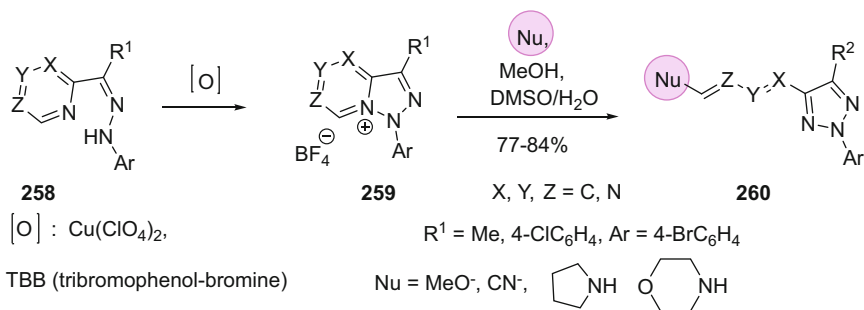
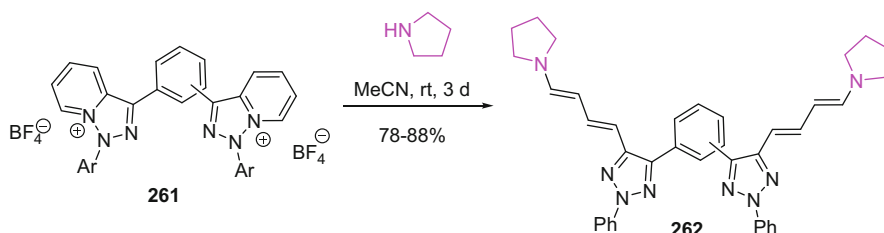
Scheme 91 Mechanism of intramolecular cyclization of 2-diazo-2-ethane imine

7 Heterocycle Transformations in the Synthesis of 2*H*-1,2,3-Triazoles

An interesting way to construct 2-aryl-1,2,3-triazoles was to use the ring-opening of bridgehead nitrogen-containing azoles yielding conjugated triazoles **260**. The starting heterocyclic salts were obtained by an oxidative cyclization of hydrazone precursor **258** (Scheme 92) [340–349].

The *m*- and *p*-phenylene-bridged bis(azolopyridinium)salts **261** were converted into the corresponding bis(dienamines) **262** by reaction with pyrrolidine (Scheme 93) [342].

A number of examples for rearrangement of 5-amino-1,2,3-thiadiazoles into 1,2,3-triazoles, also known as Dimroth rearrangement [350], have been described in detail in *Chapter 1*. In spite of the relative simplicity and the one-pot fashion of this rearrangements their preparative power to obtain various 1,2,3-triazoles is limited by the scope of the involved substrates (Schemes 92 and 93).

**Scheme 92** Ring-opening reaction of bridgehead nitrogen-containing azoles**Scheme 93** Ring-opening transformation of bis(triazolopyrimidinium) salts with pyrrolidine

8 Conclusion

This extensive review of synthetic approaches to obtain 2*H*-1,2,3-triazoles has shown that they can be classified into several distinct types.

NH-1,2,3-Triazoles and their 2-alkyl- and, rarer, 2-aryl substituted analogues can be synthesized by Huisgen azide-alkyne dipolar cycloaddition combined with postalkyl(aryl)ation or performed in a multicomponent and solid-phase fashion.

The nucleophilic substitution cannot be effectively used to obtain 2-substituted 1,2,3-triazoles since the regioselectivity of *N*-substitution is difficult to control kinetically and the N(1) atom becomes a preferred nucleophilic site under the reaction circumstances, especially for triazoles of a greater practical interest (e.g., 2-aryl and non-exchangeable N(2)-alkyl ones). It is also important to stress that acyl, sulfonyl, carbamoyl, and similar 2-substituted 1,2,3-triazoles are easily obtainable by nucleophilic substitution, but unfortunately unstable and thus did not find broad application.

Different types of cyclizations, such as oxidation, condensation, and rearrangement, occurring for arylhydrazones with an additional nitrogen-containing functional group (amidines, oximes, amidoximes) or heterocycles (1,2,4-oxadiazoles, 1,2,5-oxadiazoles, oxazoles), can also provide a convenient approach to 2-arylsubstituted 1,2,3-triazoles. Availability of substrates, convenient conditions, high yields, and regioselectivity are not the only features for this method

to be highlighted. This routine is also very useful because it provides the possibility to introduce various substituents and functional groups in order to design new materials with desired physical and biological properties.

The cumulative interest into methods of synthesis for 2*H*-1,2,3-triazoles is based on the need to develop a simple and effective synthetic approach to obtain them, as well as on the fundamental interest to the mechanistic aspects of these reactions.

References

1. Wamhoff H (1996) 1,2,3-Triazoles and their benzo derivatives. In: Katritzky AR, Rees SW, Scriven EFV (eds) *Comprehensive heterocyclic chemistry*, vol 4. Pergamon, Oxford, pp 669–732
2. Tome AC (2004) *Sci Synth* 13:415–601
3. Kosmrlj J (2012) *Click triazoles*. Springer, New York, pp 1–236
4. Krivolapov VP, Shkurko OP (2005) *Russ Chem Rev* 74(4):339–379
5. Benson FR, Savell WL (1948) *Chem Rev* 46:1–68
6. Alvarez-Builla J, Vaquero JJ, Barluenga J (2011) Five-Membered Heterocycles with Three Heteroatoms: Triazoles, *Modern heterocyclic chemistry*, vol 2. Wiley, Weinheim, pp 989–1008
7. Ramsden CA (2010) *Tetrahedron* 66:2695–2699
8. Ichino T, Andrews DH, Rathbone GJ, Misaizu F, Calvi RMD, Wren SW, Kato S, Bierbaum VM, Lineberger WC (2008) *J Phys Chem* 112:545–557
9. Elguero J, Marzin C, Roberts J (1974) *J Org Chem* 39(3):357–363
10. Rauhut G (2003) *Phys Chem Chem Phys* 5:791–800
11. Balabin RM (2009) *J Chem Phys* 131:154307–154308
12. Palmer MH, Hoffmann SV, Jones NC, Head AR, Lichtenberger DL (2011) *J Chem Phys* 134:084309–084313
13. Abound J-LM, Foces-Foces C, Notario R, Trifonov RE, Volovodenko AP, Ostrovskii VA, Alkorta I, Elguero J (2001) *Eur J Org Chem* 2001:3013–3024
14. Zhou Z, Liu R, Wang J, Li S, Liu M, Bredas J-L (2006) *J Phys Chem A* 110:2322–2324
15. Huisgen R (1984) 1,3-Dipolar cycloaddition – Introduction, survey, mechanism. In: Padwa A (ed) *1,3-Dipolar cycloaddition chemistry*, vol 1. Wiley, New York, pp 1–176
16. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB (2002) *Angew Chem Int Ed* 41:2596–2599
17. Tornøe CW, Christensen C, Meldal M (2002) *J Org Chem* 67:3057–3064
18. Liu Y, Yan W, Chen Y, Petersen JL, Shi X (2008) *Org Lett* 10(23):5389–5392
19. Yan W, Wang Q, Lin Q, Li M, Petersen JL, Shi X (2011) *Chem Eur J* 1(18):5011–5018
20. Dimtoth O, Fester G (1910) *Ber Dtsch Chem Ges* 43:2219–2223
21. Hartzel LM, Benson FR (1954) *J Am Chem Soc* 76:667–670
22. Buckler RT, Hartzler HE, Kurchacova E, Nichols G, Phillips BM (1978) *J Med Chem* 21(12):1254–1260
23. Livi O, Biagi G, Ferretti M, Lucacchini A, Barili PL (1983) *Eur J Med Chem* 18(5):471–475
24. Trybulski EJ, Benjamin L, Vitone S, Walser A, Fryer R (1983) *J Med Chem* 26(3):367–372
25. Calderone V, Giorgi I, Livi O, Martinotti E, Martelli A, Nardi A (2005) *Il Farmaco* 60(3):367–375
26. Hou D-R, Alam S, Kuan T-C, Ramanathan M, Lin T-P, Hung M-S (2009) *Bioorg Med Chem Lett* 19:1022–1025
27. Berger O, Kaniti A, van Ba CT, Vial H, Ward SA, Biagini GA, Bray PG, O'Neill PM (2011) *ChemMedChem* 6:2094–2108
28. Velezheva VS, Erofeev YV, Suvorov NN (1980) *J Org Chem USSR (English Translation)* 16(10):1839–1844

29. Tullis JS, VanRens JC, Natshus MG, Clark MP, De B, Hsieh LC, Janusz MJ (2003) *Bioorg Med Chem Lett* 13:1665–1668
30. Sobenina LN, Tomilin DN, Ushakov IA, Mikhaleva AI, Ma JS, Yang G, Trofimov BA (2013) *Synthesis* 45(5):678–682
31. Revesz LP, Di Padova FE, Buhl T, Feifel R, Gram H, Hiestand P, Manning U, Wolf R, Zimmerlin AG (2002) *Bioorg Med Chem Lett* 12:2109–2112
32. Bertha F, Giang L, Fetter J, Kajtar-Peredy M, Lempert K, Czira G (2003) *J Chem Res Synop* 759–760
33. Bertelli L, Biagi G, Calderone V, Giorgi I, Livi O, Scartoni V, Barili PL (2000) *J Heterocycl Chem* 37(5):1169–1176
34. Balle T, Perregaard J, Ramirez MT, Larsen AK, Soby KK, Liljefors T, Andersen K (2003) *J Med Chem* 46:265–283
35. Sheehan JC, Robinson CA (1949) *J Am Chem Soc* 71:1436–1440
36. Journet M, Cai D, Kowal JJ, Larsen RD (2001) *Tetrahedron Lett* 42:9117–9118
37. Zheng W, Degterev A, Hsu E, Yuan J, Yuan C (2008) *Bioorg Med Chem Lett* 18:4932–4935
38. Cheng ZY, Li WJ, He F, Zhou JM, Zhu XF (2007) *Bioorg Med Chem* 15:1533–1538
39. Jarowski PD, Wu YL, Schweizer WB, Diederich F (2008) *Org Lett* 10(15):3347–3350
40. Trofimenko S, Rheingold AL, Incarvito CD (2003) *Angew Chem Int Ed* 42:3506–3509
41. Rheingold AL, Liable-Sands LM, Trofimenko S (2000) *Angew Chem Int Ed* 112(18):3459–3462
42. Rheingold AL, Liable-Sands LM, Trofimenko S (2002) *Inorg Chim Acta* 330:38–43
43. Tanaka Y, Miller SI (1973) *J Org Chem* 38(15):2708–2712
44. Caliendo G, Fiorino F, Grieco P, Perissutti E, Santagada V, Meli R, Raso GM, Zanesco A, De Nicci G (1999) *Eur J Med Chem* 34:1043–1051
45. Taboada LH, Feist H, Suarez JQ, Michalik M, Peseke K (2004) *J Carbohydr Chem* 23(5):325–335
46. Birkofer L, Wegner P (1966) *Chem Ber* 99:2512–2517
47. Birkofer L, Wegner P (1967) *Chem Ber* 100:3485–3494
48. Richardson C, Fitchett CM, Keene FR, Steel P (2008) *Dalton Trans* 19:2534–2537
49. Kim DK, Kim J, Park HJ (2004) *Bioorg Med Chem Lett* 14(1):2401–2405
50. Kosztkovska-Stawinska M, Mironiuk-Puchalska E, Rowicki T (2012) *Tetrahedron* 68:214–225
51. Blass BE, Coburn K, Lee W, Fairweather N, Fluxe A, Wu S, Janusz JM, Murawsky M, Fadayel GM, Fang B, Hare M, Ridgeway J, White R, Jackson C, Djandjighian L, Hedges R, Wireko FC, Ritter AL (2006) *Bioorg Med Chem Lett* 16(17):4629–4632
52. Oliva CG, Jagerovic N, Goya P, Alkorta I, Elguero J, Cuberes R, Dordal A (2010) *Arkivoc* 2:127–147
53. Moltzen EK, Pedersen H, Bogeso KP, Meier E, Frederiksen K, Sanchez C, Lembel HL (1994) *J Med Chem* 37(24):4085–4099
54. Jenkins SM, Wadsworth HJ, Bromidge S, Orlek BS, Wyman PA, Riley GJ, Hawkins J (1992) *J Med Chem* 35:2392–2406
55. Regitz M, Arnold B, Danion D, Schubert H, Fusser G (1981) *Bull Soc Chim Belg* 90(6):615–632
56. Simo O, Rybar A, Alfoldi J (2000) *J Heterocycl Chem* 37(5):1033–1039
57. White AD, Purchase CF, Picard JA, Anderson MK, Mueller SB, Bocan TMA, Bousley RF, Hamelehle KL, Krause BR, Lee P, Stanfield RL, Reindel JF (1996) *J Med Chem* 39:3908–3919
58. Ye C, Gard GL, Winter RW, Syvret RG, Twamley B, Shreeve JM (2007) *Org Lett* 9(19):3841–3844
59. Wadsworth HJ, Jenkins SM, Orlek BS, Cassidy F, Clark MSG, Brown F, Riley GJ, Graves D, Hawkins J, Naylor CB (1992) *J Med Chem* 35:1280–1290
60. Saalfrank RW, Wirth U, Lurz C-J (1989) *J Org Chem* 54(18):4356–4359
61. Smith EAS, Molev G, Botoshansky M, Gandelman M (2011) *Chem Commun* 47(1):319–321

62. Mayot E, Lemiere P, Gerardin-Charbonnier C (2008) *Eur J Org Chem* 13:2232–2239
63. Shaiyany BA, Meshcheryakov VI (2001) *Russ J Org Chem* 37(12):1797–1798
64. Nabiev OG, Nabizade ZO, Kostyanovsky RG (2009) *Mendeleev Commun* 19(5):281–283
65. Jones JH, Wyatt PB (1987) *J Chem Res, Miniprint* 12:3176–3178
66. Priebe H (1987) *Acta Chem Scand B* 41(9):640–645
67. Hees U, Vogelbacher U-J, Michels G, Regitz M (1989) *Tetrahedron* 45(10):3115–3130
68. Naidorf-Meir S, Hassner A (1992) *J Org Chem* 57(19):5102–5105
69. Chhen AI, Soufiaoui M, Carrie R (1992) *Bull Soc Chim Fr* 4:308
70. Magnus P, Lacour J, Evans PA, Roe MB, Hulme C (1996) *J Am Chem Soc* 118(14):3406–3418
71. Hassner A, Stern M, Gottlieb HE, Frolov F (1990) *J Org Chem* 55(8):2304–2306
72. Achamlale S, Mabrouk H, Elachqar A, El Hallaoui A, El Hajji S, Alami A, Bellan J, Mazieres MR, Wolf JG, Pierrot M (2007) *Phosphorus. Sulfur Silicon Relat Elem* 182(2):357–367
73. Kemmerich T, Nelson JH, Takach NE, Boehme H, Jablonski B, Beck W (1982) *Inorg Chem* 21:1226–1232
74. Hsieh BT, Takach NE, Milosavljevic EB, Nelson JH, Kemmerich T, Beck W, Bresciani-Pahor N, Randaccio L, Brower KR (1987) *Inorg Chim Acta* 134(1):31–42
75. Parimal P, Sukla C, Kamalaksha N (1990) *Inorg Chim Acta* 170(1):27–35
76. Guillard R, Jagerovic N, Tabard A, Richard P, Courthaudon L, Louati A, Lecomte C, Kadish KM (1991) *Inorg Chem* 30:16–27
77. Hanssgen D, Jansen M, Leben C, Oster T (1995) *J Organomet Chem* 494(12):223–228
78. Pachhunga K, Carroll PJ, Rao KM (2008) *Inorg Chim Acta* 361:2025–2031
79. Chen C-K, Tong H-C, Hsu C-YC, Lee C-Y, Fong YH, Chuang Y-S, Lo Y-H, Lin Y-C, Wang Y (2009) *Organometallics* 28:3358–3368
80. Nongbri SL, Das B, Rao KM (2009) *J Organomet Chem* 694:3881–3891
81. Miguel-Fernandez S, Martinez de Salinas S, Diez J, Gamasa MP, Lastra E (2013) *Inorg Chem* 52(8):4293–4302
82. Herberhold M, Goller A, Milius W (2003) *Z Anorg Allg Chem* 629:1162–1168
83. Chang C-W, Lee G-H (2003) *Organometallics* 22:3107–3116
84. Ng SY, Fang G, Leong WK, Goh LY, Garland MV (2007) *Eur J Inorg Chem* 2007:452–462
85. Ponpandian T, Muthusubramanian S (2012) *Tetrahedron Lett* 53(1):59–63
86. Meek JS, Fowler JS (1968) *J Org Chem* 33:985–991
87. Meek JS, Fowler JS (1967) *J Am Chem Soc* 89:1967
88. Aboskalova NI, Smirnova NN, Kataeva ON, Baichurin RI, Fel'gendler AV, Berkova GA, Berestovitskaya VM (2008) *Russ J Gen Chem* 78(9):1711–1718
89. Bakhareva SV, Berestovitskaya VM, Aboskalova NI (2001) *Russ J Gen Chem* 71(9):1493–1494
90. Baryshnikov AT, Erashko VI, Zubanova NI, Ugrak BI, Shevelev SA (1992) *Bull. Russ Acad Sci Div Chem Sci (Engl Transl)* 41(4):958–966
91. Dong Z, Hellmund KA, Pyne SG (1993) *Aust J Chem* 46(9):1431–1436
92. Prager RH, Razzino P (1994) *Aust J Chem* 47(7):1375–1386
93. Zang Y, Parrish DA, Shreeve JM (2013) *J Material Chem* 1:585–593
94. Nitshe C, Steuer C, Klein CD (2011) *Bioorg Med Chem* 19:7318–7337
95. Zefirov NS, Chepovskaya NK, Apsalon UR (1976) *Zhurnal Organicheskoi Khimii* 12:143–148
96. Bajpai LK, Bhaduti AP (1996) *Synth Commun* 26(10):1849–1859
97. Velezhova VS, Vampilova VV, Marshakov YV, Suvorov NN (1984) *Chem Heterocycl Compd* 20(12):1392–1393
98. Zou W, Bhasin M, Vembaiyan K, Williams DT (2009) *Carbohydr Chem* 344:1024–1027
99. Kamal A, Swapna P (2013) *RSC Advances* 3(20):7419–7426
100. Schmitz E, Lutze G (1986) *Z Chem* 26(5):165–166
101. Silva AMS, Vieir JS, Cavaleiro JAS, Patonay T, Lévai A, Elguero J (1999) *Heterocycles* 51:481–488

102. Chakrasali RT, Ila H, Janjappa H (1988) *Synthesis* 453–455
103. Timoshenko VM, Nikolin YV, Chernega AN, Rusanov EB, Shermolovich YG (2001) *Chem Heterocycl Compd* 37(4):470–476
104. Bandera YP, Kanishchev OS, Timoshenko VM, But SA, Nesterenko AM, Shermolovich YG (2007) *Chem Heterocycl Compd* 43(9):1138–1147
105. Usachev BI, Usachev SA, Roeschenthaler G-V, Sosnovskikh VY (2011) *Tetrahedron Lett* 52(50):6723–6725
106. Bernard C, Ghosez L (1980) *J Chem Soc Chem Commun* 20:940–941
107. Henriët M, Houtekie M, Téchey B, Touillaux R, Ghosez L (1980) *Tetrahedron Lett* 21: 223–226
108. Maiorana S, Pocar D, Croce PD (1966) *Tetrahedron Lett* 8(48):6043–6045
109. Bianchetti G, Croce PD, Pocar D (1965) *Tetrahedron Lett* 7(25):2039–2041
110. Zanirato P (2002) *J Chem Soc Perkin Trans 1* 1420–1425
111. Adamo I, Benedetti F, Berti F, Nardin G, Norbedo S (2003) *Tetrahedron Lett* 44:9095–9097
112. Tsai C-W, Yang S-C, Liu Y-M, Wu MJ (2009) *Tetrahedron* 65:8367–8372
113. Gao Y, Lam Y (2006) *Org Lett* 8(15):3283–3285
114. Zhang Y, Li X, Li J, Chen J, Meng X, Zhao M, Chen B (2012) *Org Lett* 14(1):26–29
115. Lu L-H, Wu J-H, Yang C-H (2008) *J Chin Chem Soc* 55:414–417
116. L'abbe G, Mahy M, Bollyn M, Germain G, Scheefer G (1983) *Bull Soc Chim Belg* 92(10):881–892
117. Wang X-J, Sidhu K, Zhang L, Campbell S, Haddad N, Reeves DC, Krishnamurthy D, Senanayake CH (2009) *Org Lett* 11(23):5490–5493
118. Rohrig UF, Majjigapu SR, Grosdidier A, Bron S, Stroobant V, Pilotte L, Colau D, Vogel P, Van den Eynde BJ, Zoete V, Michielin O (2012) *J Med Chem* 55:5270–5290
119. Jin T, Kamijo S, Yamamoto Y (2004) *Eur J Org Chem* 3789–3791
120. Osawa A, Mera A, Namba K, Tanino K (2013) *Synlett* 24(2):207–211
121. Juricek M, Kouwer PHJ, Rehak J, Sly J, Rowan AE (2009) *J Org Chem* 74(1):21–25
122. Maeda C, Yamaguchi S, Ikeda C, Shinokubo H, Osuko A (2008) *Org Lett* 10(4):549–552
123. Pokrovskaya V, Belakhov V, Hainrichson M, Baasov T, Yaron S, Baasov T (2009) *J Med Chem* 52(8):2243–2254
124. Cohrt AE, Jensen JF, Nielsen TE (2010) *Org Lett* 12(23):5414–5417
125. Ulrich G, Ziesell R, Haelele A (2012) *J Org Chem* 77:4298–4311
126. Yap AH, Weinreb SM (2006) *Tetrahedron Lett* 47:3035–3038
127. Kamijo S, Jin T, Yamamoto Y (2004) *Tetrahedron Lett* 45:689–691
128. Kamijo S, Jin T, Huo Z, Yamamoto Y (2003) *J Am Chem Soc* 125:7786–7787
129. Kamijo S, Jin T, Huo Z, Yamamoto Y (2004) *J Org Chem* 69:2386–2393
130. Kamijo S, Jin T, Huo Z, Yamamoto Y (2002) *Tetrahedron Lett* 43:9707–9710
131. Kalisiak J, Sharpless KB, Fokin VV (2008) *Org Lett* 10(15):3171–3774
132. Li J, Wang D, Zhang Y, Li J, Chen B (2009) *Org Lett* 11(14):3024–3027
133. Li N, Wang D, Li J, Li C, Chen B (2011) *Tetrahedron Lett* 52:980–982
134. Keivanloo A, Bakherad M, Taheri SAN, Samangoeei S (2013) *C R Chimie* 16:239–243
135. Amantini D, Fringuelli F, Piermatti O, Pizzo F, Zunino E, Vaccaro L (2005) *J Org Chem* 70:6526–6529
136. Chen Y, Liu Y, Petersen JL, Shi X (2008) *Chem Commun* 3254–3256
137. Sengupta S, Duan H, Lu W, Petersen JL, Shi X (2008) *Org Lett* 10(7):1493–1496
138. Cristalli G, Eleuteri A, Volpini R, Vittori S, Camaioni E, Lupidi G (1994) *J Med Chem* 37(1):201–205
139. Pinto DJP, Orwat MJ, Koch S, Rossi KA, Alexander RS, Smallwood A, Wong PC, Rendina AR, Luettgen JM, Knabb RM, He K, Xin B, Wexler RR, Lam PYS (2007) *J Med Chem* 50(22):5339–5356
140. Bergstrom CP, Sloan CP, Wang HH, Parker MF, Smith DW, Zheng M, Hansel SB, Polson CT, Barber LE, Bursucker I, Guss VL, Corsa JA, Barten DM, Felsenstein KM, Roberts SB (2008) *Bioorg Med Chem Lett* 18(1):175–178

141. Johnson PS, Ryckmans T, Bryans J, Beal DM, Dack KN, Feeder N, Harrison A, Lewis M, Mason HJ, Mills J, Newman J, Pasquinet C, Rawson DJ, Roberts LR, Russell R, Spark D, Stobie A, Underwood TJ, Ward R, Wheeler S (2011) *Bioorg Med Chem Lett* 21(19): 5684–5687
142. Doiron J, Soultan AH, Richard R, Toure MM, Picot N, Richard R, Cuperlovic-Culf M, Robichaud GA, Touaibia M (2011) *Eur J Med Chem* 46:4010–4024
143. Holzer W, Brandstaetter B, Jager C, Kaun M, Langer T, Bowen WD, Wayne D (2004) *Sci Pharm* 72(3):197–211
144. Mombelli P, Le Chapelain C, Munzinger N, Joliat E, Illarionov B, Schweizer WB, Hirsch AKH, Fischer M, Bacher A, Diederich F (2013) *Eur J Org Chem* 6:1068–1079
145. Sun L, Liang C, Shirazian S, Zhou Y, Miller T, Cui J, Fukuda JY, Chu JY, Nematalla A, Wang X, Chen H, Sistla A, Luu TC, Tang F, Wei J, Tang C (2003) *J Med Chem* 46(7): 1116–1119
146. Taillefer M, Ouali A, Renard B, Spindler J-F (2006) *Chem Eur J* 12(20):5301–5313
147. Li Q, Zu Y, Shi R, Yao L, Fu Y, Yang Z, Li L (2006) *Bioorg Med Chem* 14(21):7175–7182
148. Roman G, Szarek WA, Rahman MN, Jia Z, Vukomanovic D, Nakatsu K (2010) *Chem Biol Drug Des* 75(1):68–90
149. Kochanny MJ, Adler M, Ewing J, Brain D, Griedel BD, Ho E, Ho E, Karanjawala R, Lee W, Lentz D, Liang AM, Morrissey MM, Phillips GB, Post J, Sacchi KL, Sakata ST, Subramanyam B, Vergona R, Walters J, White KA, Whitlow M, Ye B, Zhao Z, Shaw KJ (2007) *Bioorg Med Chem* 15(5):2127–2146
150. Voitekhovich SV, Gaponik PN, Lyakhov AS, Filipova JV, Sukhanova AG, Sukhanov GT, Ivashkevich OA (2009) *Tetrahedron Lett* 50(21):2577–2579
151. Ohta S, Kawasaki I, Uemura T, Yamashita M, Yoshioka T, Yamaguchi S (1997) *Chem Pharm Bull* 45(7):1140–1145
152. Seto M, Miyamoto N, Aikawa K, Aramaki Y, Kanzaki N, Iizawa Y, Baba M, Shiraishi M (2005) *Bioorg Med Chem* 13(2):363–386
153. Wang X-J, Zhang L, Krishnamurthy D, Senanayake CH, Wipf P (2010) *Org Lett* 12(20): 4632–4635
154. Barili PL (2002) *J Heterocycl Chem* 37:1169–1176
155. Iddon B, Nicolas M (1996) *J Chem Soc Perkin Trans 1* 1341–1347
156. Chen Y, Wang D, Jeffrey L, Petersen JL, Akhmedov NG, Shi X (2010) *Chem Commun* 46 (33):6147–6149
157. Wang H, Yin H (2010) *Org Process Res Dev* 14(2):474–476
158. Al-Azmi A, George P, El-Dousouqui OME (2007) *J Heterocycl Chem* 44(3):515–520
159. Pandey A, Volkots DL, Seroogy JM, Rose JW, Yu J-C, Lambing JL, Hutchaleelaha A, Hollenbach SJ, Abe K, Giese NA, Scarborough RM (2002) *J Med Chem* 45(17):3772–3793
160. Street LJ, Baker R, Davey WB, Guiblin AR, Jelley RA, Reeve AJ, Routledge H, Sternfeld F, Watt AP (1995) *J Med Chem* 38(10):1799–1810
161. Pardo C, Graf S, Ramos M, Sesmlro E, Elguero J (2000) *J Org Prep Proced Int* 32(4):385–390
162. Itoh H, Yoneda R, Tobitsuka J, Matsuhisa T, Kajino H, Ohta H, Hayashi N, Takahi Y, Tsuda M, Takeshiba H (2000) *Chem Pharm Bull* 48(8):1148–1153
163. Kitazaki T, Ichikawa T, Tasaka A, Hosono H, Matsushita Y, Hayashi R, Okonogi K, Itoh K (2000) *Chem Pharm Bull* 48(12):1935–1946
164. Nag SK, Dureja P (1997) *J Agric Food Chem* 45(1):294–298
165. Tsuruoka A, Kaku Y, Kakinuma H, Tsukada I, Yanagisawa M, Naito T (1997) *Chem Pharm Bull* 45(7):1169–1176
166. Adamson GA, Rees CW (1996) *J Chem Soc Perkin Trans 1* 13:1535–1543
167. Li J, Zhang Y, Wang D, Wang W, Gao T, Wang L, Li J, Huang G, Chen B (2010) *Synlett* 11:1617–1622
168. Papudippu M, Shu H, Izenwasser S, Wade D, Gulasey G, Fournet S, Stevens ED, Lomenzo SA, Trudell ML (2012) *Med Chem Res*. doi 10.1007/s00044-012-9991-3

169. Colombo F, Cravotto G, Palmisano G, Penoni A, Sisti M (2008) *Eur J Org Chem* 16: 2801–2807
170. Celli AM, Ferrini S, Ponticelli F (2006) *Eur J Org Chem* 13:3021–3025
171. Meshcheryakov VI, Shainyan BA, Tolstikova LL, Albanov AI (2003) *Russ J Org Chem* 39(10):1517–1521
172. Boshta NM, Bomkamp M, Schnakenburg G, Waldvogel SR (2011) *Eur J Org Chem* 10: 1985–1992
173. Boshta NM, Bomkamp M, Waldvogel SR, Schnakenburg G, Waldvogel SR (2011) *Eur J Org Chem* 1985–1992
174. Im WB, Choi SH, Park J-Y, Choi SH, Finn J, Yoon S-H (2011) *Eur J Med Chem* 46(4): 1027–1039
175. Ohnmacht S, Nava P, West R, Parker R, Atkinson J (2008) *Bioorg Med Chem* 16(16): 7631–7638
176. Ivashkevich OA, Matulis VE, Gaponik PN, Sukhanov GT, Filippova JV, Sukhanova AG (2008) *Chem Heterocycl Compd* 44(12):1472–1484
177. Butler RN, Hanniffy JM, Stephens JC, Burke LA (2008) *J Org Chem* 73(4):1354–1364
178. Lehmkuhl FA, Witkowski JT, Robins RK (1972) *J Heterocycl Chem* 9:1195–1201
179. Makabe O, Suzuki H (1977) Umezawa s. *Bull Chem Soc Jpn* 50:2689–2693
180. Shingarova ID, Lebedev AT, Prejbrazhenskaya MN (1987) *Chem Heterocycl Compd* 23:76
181. Biagi G, Ciambone F, Giorgi I, Livi O, Scartone V, Barili PL (2002) *J Heterocycl Chem* 33 (6):889–893
182. Lee K-H, Park C-E, Min K-H, Shin Y-J, Chung C-M, Kim H-H, Yoon H-J, Kim W, Ryu E-J, Shin Y-J, Nam H-S, Cho J-W, Lee H-Y (2010) *Bioorg Med Chem Lett* 20(18):5567–5571
183. Yan W, Liao T, Tuguldur O, Zhong C, Petersen JL, Shi X (2011) *Chem Asian J* 6(10): 2720–2724
184. Yan W, Wang Q, Chen Y, Petersen JL, Shi X (2010) *Org Lett* 12(15):3308–3311
185. Banda G, Srinivasulu D, Ugandhar V, Chakravarthy IE (2006) *Indian J Chem Sect 4B*(8): 1920–1923
186. Rueckle T, Biamonte M, Grippi-Vallotton T, Arkinstall S, Cambet Y, Camps M, Chabert C, Church DJ, Halazy S, Jiang X, Martinou I, Nicols A, Sauer W, Gotteland J-P (2004) *J Med Chem* 47(27):6921–6934
187. Bhanuchandra M, Kuram MR, Sahoo AK (2012) *Org Biomol Chem* 10(17):3538–3555
188. Yan W, Ye X, Weise K, Petersen JL, Shi X (2012) *J Chem Soc Chem Commun* 48(29): 3521–3523
189. Kwok SW, Hein JE, Fokin VV, Sharpless KB (2008) *Heterocycles* 76(2):1141–1154
190. Diner P, Nielsen M, Marigo M, Joergensen KA (2007) *Angew Chem Int Ed* 46(12): 1983–1987
191. Diaz-Ortiz A, Cozar A, Prieto P, Hoz A, Moreno A (2006) *Tetrahedron Lett* 47(49): 8761–8764
192. Duan H, Yan W, Sengupta S, Shi X (2009) *Bioorg Med Chem Lett* 19(14):3899–3902
193. Gonzalez J, Gonzalez J, Perez-Calleja C, Lopez LA, Vicente R (2013) *Angew Chem Int Ed* 52(22):5853–5857
194. Lesiv AV, Ioffe SL, Strelenko YA, Tartakovsky VA (2012) *Helv Chim Acta* 85(10): 3489–3507
195. Samet AV, Laichter AL, Reznikov DN, Yamskov AN, Ugrak BI, Chernyshova NB, Yolkin VV, Semenov VV (1994) *Russ Chem Bull* 43(6):1073–1078
196. Sedov AL, Nemeryuk MP, Anisimova OS, Solov'eva NP, Safonova TS (1994) *Chem Heterocycl Compd* 30(10):1187–1191
197. Kanishchev OS, Gudzh GP, Shermolovich YG, Nesterova NV, Zagorodnya SD, Golovan AV (2011) *Nucleosides. Nucleot Nucleic Acids* 30:768–783
198. Shavaleev NM, Scopelliti R, Gratzel M, Nazeeruddin M (2012) *Inorg Chim Acta* 388:84–87
199. Wertz S, Kodama S, Studer A (2011) *Angew Chem Int Ed* 50(48):11511–11515
200. Wang B, Li J, Huo H, Fan X, Fu X, Zhou C (2010) *Chin J Chem* 28(5):781–784

201. Roppe J, Smith ND, Huang D, Tehrani L, Wang B, Anderson J, Brodtkin J, Chung J, Jiang X, King C, Munoz B, Varney PP, Cosford NDP (2004) *J Med Chem* 47(19):4645–4648
202. Sapozhnikov OY, Dutov MD, Korolev MA, Kachala VV, Kadentsev VI, Shevelev SA (2004) *Russ Chem Bull* 53(3):588–595
203. Sapozhnikov OY, Dutov MD, Korolev MA, Kachala VV, Shevelev SA (2001) *Mendeleev Commun* 6:232–233
204. Jia ZJ, Wu Y, Huang W, Zhang P, Clizbe LA, Goldman EA, Sinha U, Arfsten AE, Edwards ST, Alphonso M, Hutchaleelaha A, Scarborough RM, Zhu B-Y (2004) *Bioorg Med Chem Lett* 14(14):1221–1227
205. Regueiro-Ren A, Xue QM, Swidorski JJ, Gong Y-F, Mathew M, Parker DD, Yang Z, Eggers B, D'Arienzo C, Sun Y, Malinowski J, Gao Q, Wu D, Langley DR, Colonno RJ, Chien C, Grasela DM, Zheng M, Lin P-F, Meanwell NA, Kadow JF (2013) *J Med Chem* 56(4):1656–1669
206. Mangion IK, Sherry BD, Yin J, Fleitz FJ (2012) *Org Lett* 14(13):3458–3461
207. Ueda S, Su M, Buchwald SL (2011) *Angew Chem Int Ed* 50(38):8944–8947
208. Cox CD, McGaughey GB, Bogusky MJ, Whitman DB, Ball RG, Winrow CJ, Renger JJ, Coleman PJ (2009) *Bioorg Med Chem Lett* 19(11):2997–3001
209. Cox CD, Breslin MJ, Whitman DB, Schreier JD, McGaughey GB, Bogusky MJ, Roecker AJ, Mercer SP, Bednar RA, Lemaire W, Bruno JG, Reiss DR, Harrell CM, Murphy KL, Garson SL, Doran SM, Prueksaritanont T, Anderson WB, Tang C, Roller S, Cabalu TD, Cui D, Hartman GD, Young SD, Koblan KS, Winrow CJ, Renger JJ, Coleman PJ (2010) *J Med Chem* 53(14):5320–5332
210. Wang X-J, Zhang L, Lee H, Haddad N, Krishnamurthy D, Senanayake CH (2009) *Org Lett* 11(21):5026–5028
211. Lu R-J, Tucker JA, Pickens J, Ma Y-A, Zinevitch T, Kirichenko O, Konoplev V, Kuznetsova S, Sviridov S, Brahmachary E, Khasanov A, Mikel C, Yang Y, Liu C, Wang J, Freel S, Fisher S, Sullivan A, Zhou J, Stanfield-Oakley S, Baker B, Sailstad J, Greenberg M, Bolognesi D, Bray B, Koszalka B, Jeffs P, Jeffries C, Chucholowski A, Sexton C (2009) *J Med Chem* 52(14):4481–4487
212. Baxter CA, Cleator E, Brands KMJ, Edwards JS, Reamer RA, Sheen FJ, Stewart GW, Strotman NA, Wallace DJ (2011) *Org Process Res Dev* 15(2):367–375
213. Tyurin AY, Churakov AM, Strelenko YA, Tartakovsky VA (2008) *Russ Chem Bull* 57(1):193–196
214. Tyurin AY, Smirnov OY, Churakov AM, Strelenko YA, Tartakovsky VA (2009) *Russ Chem Bull* 58(2):361–365
215. Piersanti G, Bartoccini F, Lucarini S, Cabri W, Stasi MA, Riccioni T, Borsini F, Tarzia G, Minetti P (2013) *J Med Chem* 56:5456–5463
216. Tran T-D, Pryde DC, Jones P, Adam FM, Benson N, Bish G, Calo F, Ciaramella G, Dixon R, Duckworth J, Fox DNA, Hay DA, Hitchin J, Horscroft N, Howard M, Gardner I, Jones HM, Laxton C, Parkinson T, Parsons G, Proctor K, Smith MC, Smith N, Thomas A (2011) *Bioorg Med Chem Lett* 21(8):2389–2393
217. Bartoccini F, Cabri W, Celona D, Piersanti G, Minetti P, Tarzia G (2010) *J Org Chem* 75(15):5398–5401
218. Smirnov OY, Churakov AM, Strelenko YA, Tartakovsky VA (2008) *Russ Chem Bull* 57(10):2180–2184
219. Minetti P, Tinti MO, Carminati P, Castorina M, Di Cesare MA, Di Serio S, Gallo G, Ghirardi O, Giorgi F, Giorgi L, Piersanti G, Bartoccini F, Tarzia G (2006) *J Med Chem* 48(22):6887–6896
220. Jorg M, Shonberg J, Mak FS, Miller ND, Yuriev E, Scammells PJ, Capuano B (2013) *Bioorg Med Chem Lett* 23(11):3427–3433
221. Enguehard C, Allouchi H, Gueffier A, Buchwald SL (2003) *J Org Chem* 68(14):5614–5617
222. Hagan DJ, Gimenez-Arnau E, Schwalbe CH, Stevens MFG (1997) *J Chem Soc Perkin Trans 1* 18:2739–2746

223. Lucca GVD, Kim UT, Liang J, Cordova B, Klabe RM, Gaber S, Bacheler LT, Lam GN, Wright MR, Logue KA, Erickson-Viitanen S, Ko SS, Trainor GL (1998) *Med Chem* 41(13):2411–2423
224. Wang T, Yang Z, Zhang Z, Gong Y-F, Riccardi KA, Lin P-F, Parker DD, Rahematpura S, Mathew M, Zheng M, Meanwell NA, Kadow JF, Bender JA (2013) *Bioorg Med Chem Lett* 23(1):213–217
225. Poirier M, Goudreau S, Poulin J, Savoie J, Beaulieu PL (2010) *Org Lett* 12(10):2334–2337
226. Lu R-J, Tucker JA, Zinevitch T, Kirichenko O, Konoplev V, Kuznetsova S, Sviridov S, Pickens J, Tandel S, Brahmachary E, Yang Y, Wang J, Freel S, Fisher S, Sullivan A, Zhou J, Stanfield-Oakley S, Greenberg M, Bolognesi D, Bray B, Koszalka B, Jeffs P, Khasanov A, Ma YA, Jeffries C, Liu C, Proskurina T, Zhu T, Chucholowski A, Li R, Sexton C (2007) *J Med Chem* 50(26):6535–6544
227. Bender JA, Yang Z, Eggers B, Gong Y-F, Lin P-F, Parker DD, Rahematpura S, Zheng M, Meanwell NA, Kadow JF (2013) *Bioorg Med Chem Lett* 23(1):218–222
228. Andriani G, Amata E, Beatty J, Clements Z, Coffey BJ, Courtemanche G, Devine W, Erath J, Juda CE, Wawrzak Z, Wood JT, Lepesheva GI, Rodriguez A, Pollastri MP (2013) *J Med Chem* 56(6):2556–2567
229. Nongbri SL, Therrien B, Rao KM (2011) *Inorg Chim Acta* 376:428–436
230. Vereshchagin LI, Verkhozina ON, Pokatilov FA, Proidakov AG, Kizhnyaev VN (2010) *Chem Heterocycl Compd* 46(2):206–211
231. Velezheva VS, Marshakov VY, Mel'man AI, Kurkovskaya LN, Suvorov NN (1988) *Zhurn Org Khim* 24(7):1531
232. Kurkovskaya LN, Velezheva VS, Sorokina IK, Dmitrevskaya LI, Zhil'nikov VG (1988) *J Org Chem USSR (English Translation)* 24:1387
233. Grimster N, Zhang L, Fokin VV (2010) *J Am Chem Soc* 132(8):2510–2511
234. Yamauchi M, Miura T, Murakami M (2010) *Heterocycles* 80(1):177–181
235. Rodios NA, Alexandrou NE (1979) *J Heterocycl Chem* 16:571–575
236. El Khadem H, Shaban MAE, Nassr MAM (1970) *J Chem Soc C* 16:2167–2168
237. Bauer H, Boulton AJ, Fedeli W, Katritzky AR, Majid-Hamid A, Mazza F, Vaciago A (1972) *J Chem Soc Perkin Trans II* 662–667
238. Balachandran KS, Hirayakkanavar I, George MV (1975) *Tetrahedron* 31:1171–1177
239. Rodios NA (1984) *J Heterocycl Chem* 21:1169–1173
240. Bagramov GG, Bagramova MD (1998) *Russ Chem Bull* 47(1):192
241. Kuznetsova LM, Kuznetsov MA, Schantl JG (2000) *Russ J Org Chem* 36(6):836–842
242. Kuznetsov MA, Kuznetsova LM, Schantl JG, Wurst K (2001) *Eur J Org Chem* 7:1309–1314
243. Trofimov BA, Myachina GF, Ermakova TG, Kuznetsova NP, Volkova LI, Sultangareev RG, Larina LI, Klyba LV, Sukhanov GT, Sakovich GV (2009) *Russ J Org Chem* 45(11):1683–1685
244. Guru MM, Punniyamurthy T (2012) *J Org Chem* 77(11):5063–5073
245. Matter H, Schudok M, Schwab W, Thorwart W, Barbier D, Billen G, Haase B, Neises B, Weithmann K-U, Wollmann T (2002) *Bioorg Med Chem* 10(11):3529–3544
246. Chevallier F, Blin T, Nagaradja E, Lassagne F, Roisnel T, Halauko YS, Matulis VE, Ivashkevich OA, Mongin F (2012) *Org Biomol Chem* 10(25):4878–4885
247. Tang W-J, Hu Y-Z (2006) *Synth Commun* 36(17):2461–2468
248. Shi H, Liu F-M, Shen S-W (2011) *Phosphorus Sulfur Silicon Relat Elem* 186(2):263–270
249. Sallam MAE (2010) *Carbohydr Res* 345:341–345
250. Sallam MAE, Megid SMEA, Townsend LB (2001) *Carbohydr Res* 330(1):53–63
251. El-Sekily MA, Elba ME, Fouad FS (2000) *J Indian Chem Soc* 77(3):168–171
252. Bhattacharya A, Prasad AK, Maity J, Himanshu RT, Poonam, Olsen CE, Gross RA, Parmar VS (2003) *Tetrahedron* 59(51):10269–10277
253. Prasad AK, Bhattacharya HA, Olsen CE, Parmar VS (2002) *Bioorg Med Chem* 10(4):947–951

254. Himanshu TR, Olsen CE, Errington W, Parmar VS, Prasad AK (2002) *Bioorg Med Chem* 10(4):963–968
255. Prasad AK, Shakil NA, Himanshu NAS, Parmar VS (2001) *Pure Appl Chem* 73(1):167–174
256. Mitchel WR, Paton RM (2010) *Arkivoc* 10:34–54
257. Liu W, Li Y, Xu B, Kuang C (2013) *Org Lett* 15(10):2342–2345
258. Luo Y, Hu Y (2003) *Synth Commun* 33(20):3513–3517
259. Zhang H, Ryono DE, Devasthale P, Wang W, O'Malley K, Farrelly D, Gu L, Harrity T, Cap M, Chu C, Locke K, Zhang L, Lippy J, Kunselman L, Morgan N, Flynn N, Moore L, Hosagrahara V, Zhang L, Kadiyala P, Xu C, Dowsyko AM, Bell A, Chang C, Muckelbauer J, Zahler R, Hariharan N, Cheng PTW (2009) *Bioorg Med Chem Lett* 19:1451–1456
260. Uhlmann P, Felding J, Veds P, Begtrup M (1997) *J Org Chem* 62:9177–9181
261. Begtrup M (1982) *J Chem Soc Perkin Trans 1* 11:2749–2756
262. Henning N, Dassler T, Jugelt W (1982) *Z Chem* 22(1):25
263. Armani V, Dell'Erba C, Novi M, Petrillo G, Tavani C (1997) *Tetrahedron* 53(5):1751–1758
264. Boddy IK, Briggs GG, Harrison RP, Jones TH, O'Mahony MJ, Marlow ID, Roberts BG, Willis RJ, Bardsley R, Reid J (1996) *Pestic Sci* 48(2):189–196
265. Shafeev MA, Al'mukhamedov AA, Shcherbakov VV, Gareev GA, Vereshchagin LI (1994) *Russ J Org Chem* 30:980–984
266. Godovikova TI, Vozchikova SA, Ignat'eva EL, Khmel'nitskii LI, Korsunskii BL (2003) *Chem Heterocycl Compd* 39(5):608–612
267. Hadjiantoniou-Maroulis CP, Ikonomou V, Parisopoulou E (1996) *J Heterocycl Chem* 33:655–658
268. Begtrup M, Holm J (1981) *J Chem Soc Perkin Trans 1* 2:503–513
269. Belskaya NP, Bakulev VA, Dehaen W (2010) *Arkivoc* 16(1):275–332
270. Belskaya NP, Demina MA, Sapognikova SG, Fan Z-J, Zhang H-K, Dehaen W, Bakulev VA (2008) *Arkivoc* 2008(16):9–21
271. Demina MA, Belskaya NP, Bakulev VA (2007) *Chem Heterocycl Compd* 43(5):671–672
272. Schafer H, Gewald K (1991) Bellman P, und Gruner M. *Monatsh Chem* 122:195–207
273. Elnagdy MH, Elghandour AHH, Harb AFA, Hussien AHM, Metwally SAM (1994) *Heterocycles* 38(4):739–750
274. Richter E, Taylor EC (1956) *J Chem Soc* 78:5848–5852
275. Winterwerber M, Geiger R, Otto H-H (2006) *Monatsh Chem* 137(10):1321–1347
276. Invidiata FP, Aiello S, Furno G, Aiello EJ (2000) *Heterocycl Chem* 37:355–361
277. Al-Mousawi SM, Moustafa MS, Elnagdi MH (2007) *J Chem Res Synop* 9:515–518
278. Behbehani H, Ibrahim HM, Makhseed S (2010) *Arkivoc* 2:267–282
279. Al-Matar HM, Riyadh SM, Elnagdi MH (2007) *Arkivoc* 13:53–62
280. Riyadh SM, Al-Matar HM, Elnagdi MH (2008) *J Heterocycl Chem* 45(4):975–979
281. Behbehani H, Ibrahim HM, Makhseed S, Mahmoud H (2011) *Eur J Med Chem* 46:1813–1820
282. Abdallah TA, Salaheldin AM, Radwan NF (2007) *Z Naturforsch B Chem Sci* 62(2):261–266
283. Sutherland HS, Blaser A, Kmentova I, Franzblau SG, Wan B, Wang Y, Ma Z, Palmer BD, Denny WA, Thompson AM (2010) *J Med Chem* 53:855–866
284. Mogilaiah K, Prashanthi M, Kavitha S, Reddy NV (2005) *J Chem Res Synop* 8:523–525
285. Nikitin VM, Zavodov AV, Vereshchagin AL, Vereshchagin LI (1992) *J Org Chem USSR* 28:1885–1892
286. Kirillova LP, Shul'gina VM, Shafeev MA, Al'mukhamedov AA, Vereshchagin LI (1996) *Russ J Org* 32(7):1051–1054
287. Makhseed S, Hassaneen HME, Elnagdi MH (2007) *Z Naturforsch B Chem Sci* 62(4):529–536
288. El-Dusouqui OME, Abdelkhalik MM, Al-Awadi NA, Dib HH, George BJ, Elnagdi MH (2006) *J Chem Res Synop* 5:291–298
289. Ibrahim HM, Makhseed S, Abdel-Motaleb RM, Abdel-Salam MAM, Elnagdi MH (2007) *Heterocycles* 71(9):1951–1966
290. Aziz SI, Anvar HF, Fleita DH, Elnagdi MH (2007) *J Heterocycl Chem* 44(3):725–729

291. Hassan HHAM, El-Husseiny AHF (2001) Nucleosides. *Nucleot Nucleic Acids* 20(9): 168–1690
292. Berghot MA, Almuaikel NS (2004) Phosphorus. *Sulfur Silicon Relat Elem* 179:1907–1922
293. Ram L, Prasad SB (2001) *J Indian Chem Soc* 78(2):101–102
294. Mohareb RM, El-Omran FA, Ho JZ (2001) *Heteroat Chem* 12(3):168–175
295. D'Anna F, Frenna V, Lanza CZ, Macaluso G, Marullo S, Spinelli D, Spisani R, Petrillo G (2010) *Tetrahedron* 66(29):5442–5450
296. Frenna V, Vivona N, Spinelli D, Consiglio G (1980) *J Heterocycl Chem* 17:861–864
297. Frenna V, Buscemi S, Spinelli D, Consiglio G (1990) *J Chem Soc Perkin Trans 2* 2:215–221
298. Guernelli S, Meo PL, Morganti S, Noto R, Spinelli D (2007) *Tetrahedron* 63(41): 10260–10268
299. Fontana A, Guernelli S, Meo PL, Mezzina E, Morganti S, Noto R, Rizzato E, Spinelli D, Zappacosta R (2008) *Tetrahedron* 64(4):733–740
300. Frenna V, Vivona N, Consiglio G, Spinelli D (1984) *J Chem Soc Perkin Trans 2*(3):541–545
301. Cosimelli B, Frenna V, Guernelli S, Lanza CZ, Macaluso G, Petrillo G, Spinelli D (2002) *J Org Chem* 67(23):8010–8018
302. D'Anna F, Ferroni F, Frenna V, Guernelli S, Lanza CZ, Macaluso G, Pace V, Petrillo G, Spinelli D, Spisani R (2005) *Tetrahedron* 61(1):167–178
303. Bottoni A, Frenna V, Lanza CZ, Macaluso G, Spinelli D (2004) *J Phys Chem A* 108(10): 1731–1740
304. Mezzina E, Spinelli D, Lamartina L, D'Anna F, Frenna V, Macaluso G (2005) *Eur J Org Chem* 3980–3986
305. Buscemi S, Pace A, Piccionello AP, Pibiri I, Vivona N, Giorgi G, Mazzanti A, Spinelli D (2006) *J Org Chem* 71(21):8106–8113
306. Zhou J-X, Wong FF, Chen C-Y, Yeh M-Y (2006) *Bull Chem Soc Jpn* 79(4):644–648
307. Belskaya NP, Koksharov AV, Lesogorova SG, Slepukhin PA, Bakulev VA (2011) *Russ Chem Bull* 60:889–895
308. D'Anna F, Marullo S, Vitale P, Noto R (2011) *Eur J Org Chem* 28:5681–5689
309. Cosimelli B, Guernelli S, Spinelli D (2001) *J Org Chem* 66(18):6124–6129
310. Abdel-Khalik MM, Agamy SM, Elnagdi MH (2000) *Zeitschrift Naturforsch B Chem* 55(12): 1211–1215
311. Ghozlan SAS, Abdelhamid IA, Ibrahim HM, Elnagdi MH (2006) *Arkivoc* 15:53–60
312. Frenna V, Vivona N, Spinelli D, Consiglio G (1981) *J Heterocycl Chem* 18:723–725
313. Buscemi S, Frenna V, Vivona N, Spinelli D (1993) *J Chem Soc Perkin Trans 1* 2491–2493
314. D'Anna F, Frenna V, Macaluso G, Morganti S, Nitti P, Pace V, Spinelli D, Spisani R (2004) *J Org Chem* 69(25):8718–8722
315. Al-Zaydi KM, Borik RM, Elnagdi MH (2003) *Molecules* 8(12):910–923
316. D'Auria M, Frenna V, Marullo S, Racioppi R, Spinelli D, Viggiani L (2012) *Photochem Photobiol Sci* 11(8):1383–1388
317. D'Anna F, Frenna V, Marullo S, Noto R, Spinelli D (2008) *Tetrahedron* 64(49):11209–11217
318. D'Anna F, Frenna V, Guernelli S, Macaluso G, Marullo S, Spinelli D (2008) *J Phys Org Chem* 21(4):306–314
319. Van Arnum SD, Niemczykapi HJ (2009) *J Heterocycl Chem* 46(5):909–913
320. Starosotnikov AM, Vinogradov VM, Kachala VV, Shevelev SA (2002) *Russ Chem Bull* 51(8):1519–1522
321. Zaitsev AA, Dalinger IL, Starosotnikov AM, Kachala VV, Strelenko YA, Shkineva TK, Shevelev SA (2005) *Russ J Org Chem* 41(10):1507–1515
322. Pena-Gallego A, Rodriguez-Otero J, Cabaleiro-Lago EM (2004) *J Org Chem* 69:7013–7017
323. Molotov SI, Kulikov AS, Strelenko YA, Makhova NN, Lyssenko KA (2003) *Russ Chem Bull* 52(8):1829–1834
324. Ovchinnikov IV, Epishina MA, Molotov SI, Strelenko YA, Lyssenko KA, Makhova NN (2003) *Mendeleev Commun* 13(6):272–275

325. Molotov SI, Epishina MA, Kulikov AS, Nelyubina YV, Lyssenko KA, Suponitsky KY, Makhova NN (2006) *Mendeleev Commun* 16(5):259–262
326. Makhova NN, Ovchinnikov IV, Kulikov AS, Molotov SI, Baryshnikova EL (2004) *Pure Appl Chem* 76(9):1691–1703
327. Katritzky AR, Gordeev MF (1993) *Heterocycles* 35(1):483–513
328. Shevtsova IA, Tyrkov AG (2007) *Russ J Org Chem* 43(11):1742–1744
329. Ladyzhnikova TD, Tyrkov AG, Altukhov KV, Berkova GA (1993) *Russ J Org Chem* 29: 51–54
330. Danoun S, Baziard-Mouysset G, Stigliani J-L, Commenges G, Carpy A, Payard M (1995) *Bull Soc Chim Fr* 132:943–951
331. Saladino R, Stasi L, Nicoletti R, Crestini C, Botta M (1999) *Eur J Org Chem* 1999(11): 2751–2755
332. Perrocheau J, Carrie R, Fleury J-P (1994) *Can J Chem* 72(12):2458–2467
333. Grundon MF, Khan EA (1988) *J Chem Soc Perkin Trans 1* 2917–2919
334. Al-Azmi A, George P, El-Dusouqui OME (2007) *Heterocycles* 71(10):2183–2201
335. Morzherin YY, Kolobov MY, Mokrushin VS, Brauer M, Anders E, Bakulev V (2000) *Chem Heterocycl Chem* 36(1):22–36
336. Polak M, Vercek B (2000) *Synth Commun* 30(16):2863–2871
337. Fabian WMF, Bakulev VA, Kappe CO (1998) *J Org Chem* 63:5801–5805
338. Birny DM (1996) *J Org Chem* 61:243–251
339. Crawford M-J, Karaghiosoff K, Klapotke TM, Martin FA (2009) *Inorg Chem* 48(4): 1731–1743
340. Robbins TF, Qian H, Su X, Hughes RP, Aprahamian I (2013) *Org Lett* 15(10):2386–2389
341. Batori S, Gacs-Baitz E, Bokotey S, Messmer A (2003) *Tetrahedron* 59(24):4297–4302
342. Kotschy A, Farago J, Csampai A, Smith DM (2004) *Tetrahedron* 60:3421–3425
343. Nagy I, Konya D, Riedl Z, Kotschy A, Timari G, Messmer A, Hajos G (2003) *Tetrahedron* 59:7485–7489
344. Abarca B, Ballesteros R, Chadlaoui M, Miralles J, Murillo JV, Colonna D (2001) *Tetrahedron* 57(51):10111–10118
345. Beres M, Hajos G, Riedl Z, Timari G, Messmer A, Holly S, Shantl LG (1997) *Tetrahedron* 53(27):9393–9400
346. Beres M, Hajos G, Riedl Z, Timari G, Messmer A (1998) *Monatsh Chem* 129(8–9):897–908
347. Jones G, Richardson CM, Yates PC, Hajos G, Timari G (1993) *Tetrahedron* 49(20): 4307–4314
348. Asensio A, Abarca B, Jones G, Hursthouse MB, Malik KMA (1993) *Tetrahedron* 49(3): 703–712
349. Riedl S, Hajos G, Messmer A, Kollenz G (1993) *J Heterocycl Chem* 30(30):819–823
350. Morzherin YY, Glukhareva TV, Bakulev VA (2003) The rearrangement and transformations of 1,2,3-thiadiazoles in the organic synthesis. *Chem Heterocycl Compd* 39(6):679–706

Top Heterocycl Chem (2015) 40: 117–166

DOI: 10.1007/7081_2014_124

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Published online: 5 March 2014

Biological Properties of 1*H*-1,2,3- and 2*H*-1,2,3-Triazoles

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Patricia Garcia Ferreira, and Vitor F. Ferreira

Abstract Triazoles, which are an important class of heterocyclic compounds, have been studied for over a century and continue to attract considerable attention because of their broad range of biological activities. More recently, there has been significant interest in the development of novel triazoles with anti-inflammatory, antiplatelet, antimicrobial, antimycobacterial, antitumoral, and antiviral properties and activity against several neglected diseases. In this chapter, we covered some important biological properties of the 1*H*-1,2,3- and 2*H*-1,2,3-triazoles.

Keywords Biological activity · Cancer · Chagas' disease · Diabetes · Diseases · Triazoles · Tuberculosis

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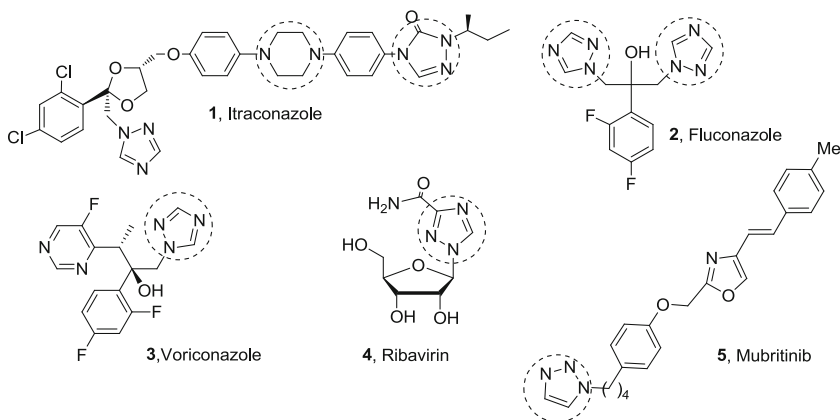


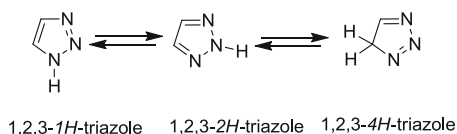
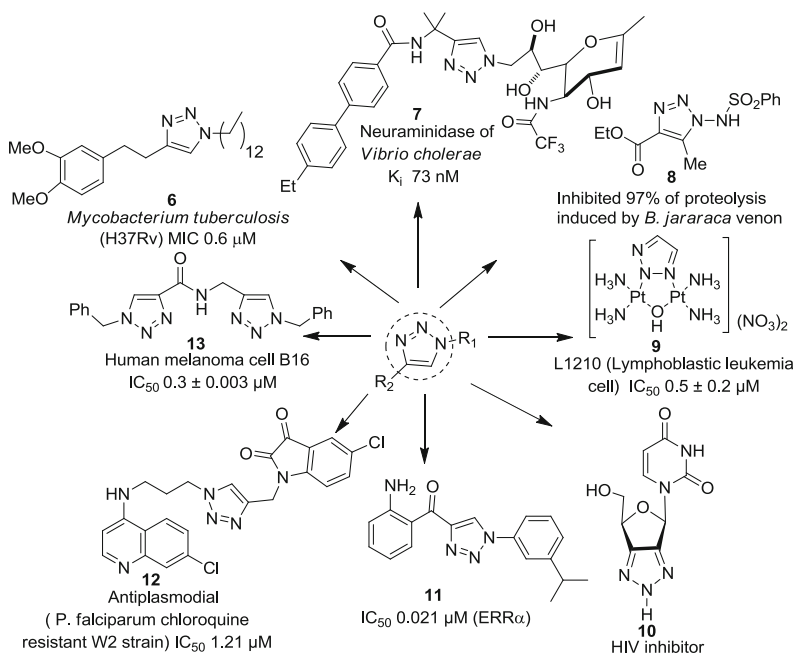
Fig. 1 Drugs having triazole rings available in their therapeutic arsenal

1 Introduction

The 1*H*-1,2,3- and 2*H*-1,2,3-triazoles have been studied for many years as an important class of heterocyclic compounds, and they continue to attract considerable attention due to their use in several applications, such as organocatalysis [1–5], in ionic liquids [6], in a broad range of biological activities, including anti-inflammatory, antiplatelet, antimicrobial [7], antitubercular, antitumoral, and antiviral as well as activities against several neglected diseases. Because of the success of several members of the triazole family that have entered the pharmaceutical market [8], many companies and research groups have shown interest in developing new methods of synthesis and screening of their biological activities [9]. Figure 1 shows that 1,2,3-1,2,4-triazoles are commonly used as drugs for the treatment of various diseases. For example, antifungal drugs containing the triazole ring include the following: (1) itraconazole, (2) fluconazole, (3) voriconazole, (4) [10] the anti-viral drug ribavirin, and (5) mubritinib (used for breast, bladder, kidney, and prostate cancers) (Fig. 1). Note that ribavirin (4) [11, 12] became a reference [13] drug for the treatment of viral infections, such as respiratory, herpes, and hepatitis [14].

The 1,2,3-triazoles are five-membered rings with three nitrogens in the ring. The triazoles that are unsubstituted at the nitrogen may exist in a tautomeric equilibrium in three structures, as shown in Scheme 1 [15].

This chapter emphasizes the recent advances in the biological activities of novel 1*H*-1,2,3- and 2*H*-1,2,3-triazole derivatives and their potential in the development of new chemical entities and new pharmaceuticals. Due to the broad biological activities of the triazoles, this chapter will emphasize their bioactive potential on tuberculosis, *Trypanosoma cruzi*, cancer cells, and glucosidase enzymes. However, 1,2,3-triazoles have shown many important biological properties, such as antibacterial [16, 17], antifungal [18–20], antiviral [21–23], β -lactamase [24], antiepileptic [25], antiplatelet [26, 27], schizophrenia [28], anti-inflammatory [29–32], anti-allergic [33–36],

**Scheme 1** Tautomeric equilibrium in the 1,2,3-triazole series**Scheme 2** Selected examples of bioactive 1,2,3-triazole derivatives

antimicrobial [37–42], anti-viral [43], anticonvulsants [44], tripanocidal [45, 46], antileishmanial [47, 48], anhydrase and protease inhibitors [49–51], anti-Alzheimer [52], cyclooxygenase [53], NO production inhibitors [54], anticaspase-3 [55] fatty acid synthase [56], antimycobacterial (6) [57], *Vibrio cholerae* (7) [58, 59], hemolysis (8) [60], leukemia L1210 (9), anti-HIV (10) [61], snake venom [62], breast cancer, phytotoxicity [63], and antiplasmodial (12) [64] (Scheme 2).

2 General Remarks

Currently, there are four 1*H*-1,2,3-triazoles in clinical trials that may become new drugs in the next few years (Fig. 2). These triazoles are the following: tazobactam (14, antibiotic) [65, 66], cefatrizine (15, anticancer) [67], carboxyamidotriazole or

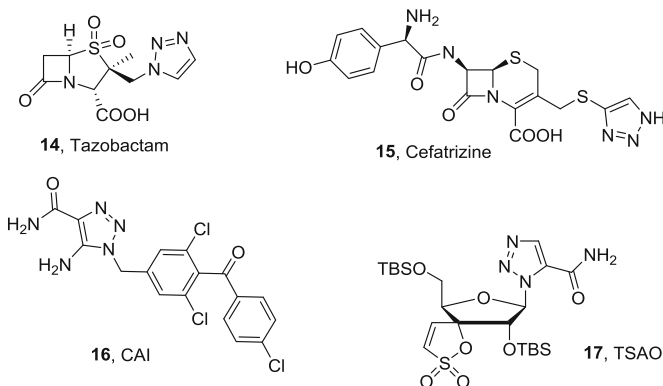


Fig. 2 1H-1,2,3-triazoles currently under clinical trials

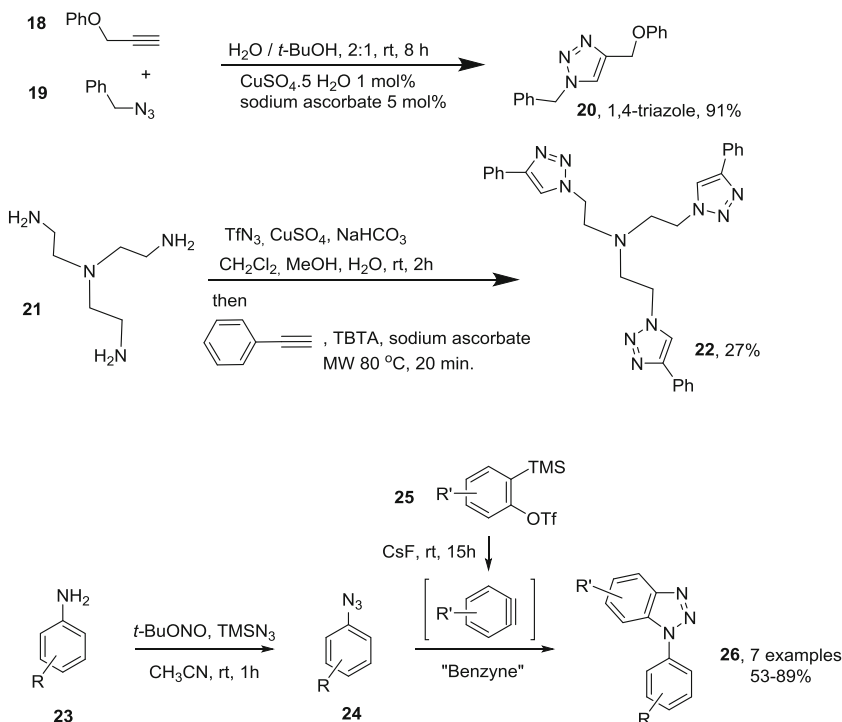
CAI (**16**, anticancer) [68], and *tert*-butyldimethylsilylspiroaminooxathioledioxide or TSAO (**17**, HIV reverse transcriptase inhibitor) [69, 70].

There are several procedures available for the preparation of 1H-1,2,3-triazoles [71–75], particularly those in which a 1H-1,2,3-triazole is incorporated into compounds containing other heterocyclic rings [76–79]. However, the interest in this class of compounds in medicinal chemistry began to increase after the publication by Sharpless and coworkers that adapted the Huisgen 1,3-dipolar cycloaddition reaction [80–83] to obtain a selective preparation of the 1,4-disubstituted triazole adduct using copper (I) as the catalyst [84] or the 1,5-disubstituted triazole using a ruthenium catalyst [85].

The Huisgen 1,3-dipolar cycloaddition reaction is a highly atom-economic and efficient coupling reaction that is especially useful for the construction of complex macrocycles [86]. Several original papers and reviews have been published recently describing Sharpless' catalytic methodology under several reaction conditions, [87] in several solvents [88–91], using different combinatorial processes [92], and describing the mechanism of the reaction [93] and biological activities (e.g., **20** and **22**) [94]. Another important procedure is the preparation of 1,2,3-1H-triazole derivatives described by Zhang and Moses [95] that showed an efficient synthesis of substituted benzotriazoles (**26**) using an azide-alkyne 1,3-dipolar cycloaddition via benzyne intermediates. Additionally, the method using a diazo transfer reaction to an amine cycloaddition reaction under copper (I) catalysis in a two-step, one-pot reaction has also proven to be effective (Scheme 3) [96].

1-Aryl-1,4,5-trisubstituted 1,2,3-1H-triazole derivatives can also be easily obtained via a one-pot three-component reaction involving boronic acids, sodium azide, and active methylene ketones [97].

Certain authors have speculated that 1,2,3-triazoles offer an appealing structural motif for peptidomimetic research because their structural and electronic characteristics are similar to those of a peptide bond [69, 98, 99]. The triazole ring can be considered a bioisostere of the amide group because these moieties have a similar H–bond acceptor capacity, a similar distance between substituents (3.8–3.9 Å in



Scheme 3 Preparation of 1,2,3-1*H*-triazole derivatives by Sharpless' methodology and a diazo transfer reaction

amides and 5.0–5.1 Å in triazoles), and a similar dipolar character (amide 4.0 Debye; triazole 5.0 Debye) [83, 100]. In addition, the ability of the 1,2,3-triazoles to participate in hydrogen bonding and dipole interactions [101] may favor binding to biomolecular targets and improve their solubility [102, 103]. The 1,2,3-triazoles are very stable under basic and acidic hydrolysis and reductive and oxidative conditions, indicative of a high aromatic stabilization [104, 105]. All of these studies demonstrate that the 1*H*-1,2,3-triazoles can display different bioactive profiles when properly functionalized [83, 106, 107].

The 2*H*-1,2,3-triazoles represent another important class of 1,2,3-triazoles that can also be prepared by several synthetic routes [108–113], but most of the routes are complex and present few opportunities to explore their biological diversity. The 2*H*-1,2,3-triazoles have diverse applications, such as anesthetic (27) [114], antiarrhythmic (28) [115], and antitubercular (29) activities [116], among others. Recently, several patents were filed regarding a family of compounds containing the 2*H*-1,2,3-triazole nucleus (30) that are involved in pharmaceutical formulations to treat Duchenne muscular dystrophy, Becker muscular dystrophy or cachexia, and (31) asthma [117] or rhinitis (Fig. 3) [118]. Preparation of 4,5-disubstituted 1,2,3-(*NH*)-triazoles can be achieved by an efficient one-pot

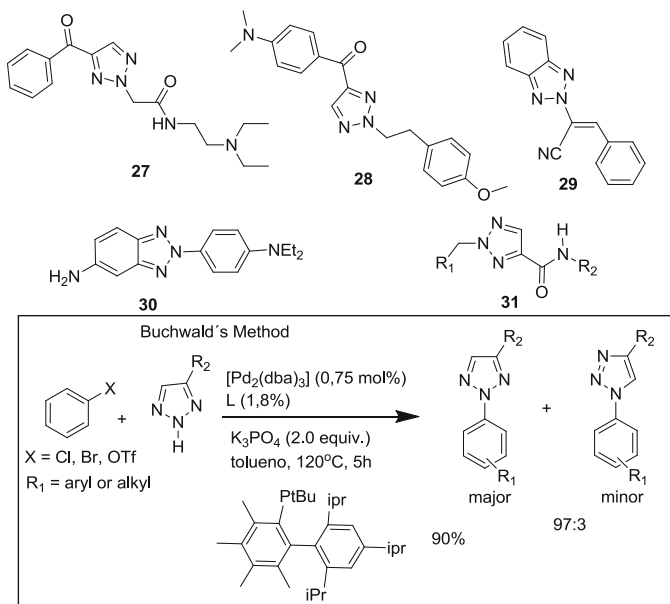


Fig. 3 Synthesis of 2*H*-1,2,3-triazole by Buchwald's method

cross-coupling/1,3-dipolar cycloaddition sequence starting from various acid chlorides, terminal alkynes, and sodium azide in the presence of silica supported-zinc bromide under aerobic conditions [119]. Buchwald and coworkers have developed a regioselective methodology (see box in Fig. 3) to add an aryl group to unsubstituted and substituted 2*H*-*N* triazoles in high yields. This method of preparation of 2*H*-1,2,3-triazoles is versatile and uses the coupling between aryl halides and the NH bond catalyzed by palladium complexes (Fig. 3) [120].

3 Tuberculosis

Many reports in the literature have shown that 1,2,3-triazoles display antimicrobial activity against several bacteria [121], especially against the *Mycobacterium tuberculosis*.

Tuberculosis (TB) is a highly infectious disease that has been affecting humans and animals for millennia. TB is highly contagious and begins with a bacterial infection in the lungs that spreads through the air causing a high level of mortality and morbidity. The challenge to discover new active compounds with low toxicity for use primarily on multi-drug resistant strains continues globally [122].

TB in humans is caused by several *Mycobacteria*, with *M. tuberculosis* being the primary bacillus causing the disease. TB can be asymptomatic in healthy individuals whose immune systems are able to block the action of the bacteria; however, in

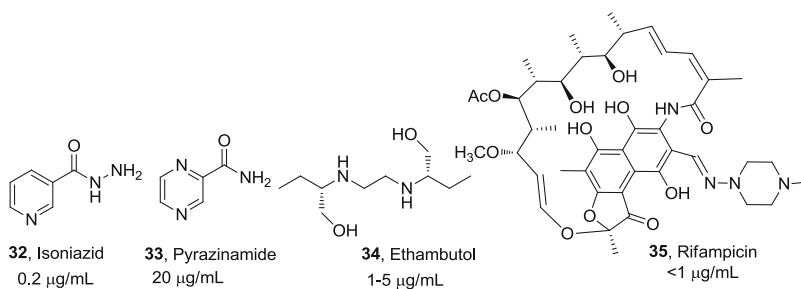


Fig. 4 Drugs primarily used against tuberculosis

most people, its symptoms include cough, fever, chest pains, weakness, weight loss, and night sweats. An estimated 70% of the population in poor countries are infected with *M. tuberculosis*, and approximately 8.8 million new cases occur annually, leading to the death of 1.4 million people [123–125]. Although the incidence of TB has been decreasing, recent statistics have shown alarming numbers of new infections. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV), and 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430,000 deaths among people who were HIV-positive [126]. The high rate of occurrence of this disease in poor countries is closely related to poor living conditions and the spread of the HIV-virus.

Strains of *M. tuberculosis* that are resistant to the old and new drugs on the market present a serious problem. These strains have been systematically detected in countries that do not emphasize public health and fail to heed recommendations regarding the importance of treatment adherence. Therefore, the cost for the treatment of drug resistant TB is growing, and there is an alarming weakness in the medical armamentarium.

The primary treatment for TB uses a combination of the following four drugs: isoniazid (32), pyrazinamide (33), ethambutol (34), and rifampicin (35) (Fig. 4). The intention of using this combination of existing drugs is to increase patient adherence to the treatment and, thus, to avoid the emergence of new resistant strains of bacteria that utilize different mechanisms of action. Rifampicin (35) inhibits the biosynthesis of RNA polymerase, isoniazid (32) inhibits mycolic acid synthesis, pyrazinamide (33) inhibits cell membrane synthesis, and ethambutol (34) inhibits cell-wall biosynthesis. However, these older drugs have severe side effects, and various strains of bacteria have developed resistance to them. Therefore, the development of new and more efficient drugs that act on other targets of *M. tuberculosis* is imperative [127–130].

Some of the new compounds have completed phase I clinical trials and are being evaluated in phase II trials in humans with TB to determine their safety, tolerability, efficacy, pharmacokinetics, and dosing regimen. If these candidates pass to phase II, they will proceed to phase III trials (Fig. 5).

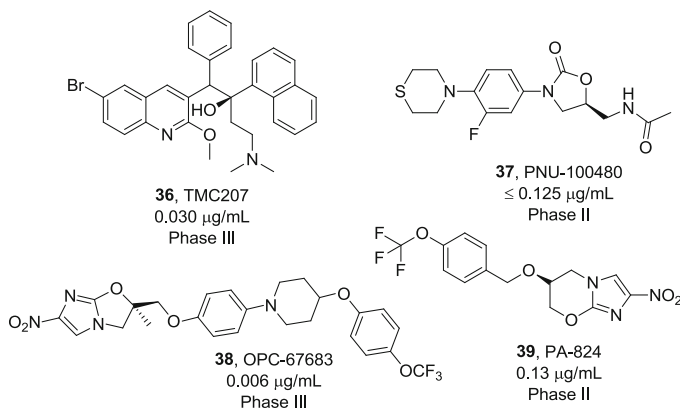
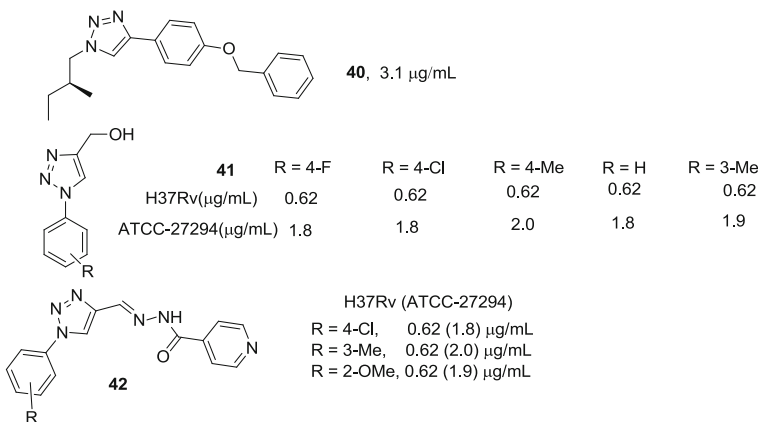


Fig. 5 New candidates for anti-TB drugs that are in phases II and III [131–134]

Because the population of the resistant new strains of *M. tuberculosis* continues to grow, the search for new lead compounds, preferably ones that can act on innovative targets, is urgent. Several research programs have focused on the search for new inhibitors of *M. tuberculosis*. These new *M. tuberculosis* growth inhibitors include compounds with unknown mechanisms of action and others whose mechanisms of action are known, such as the glycopeptidolipids, which affect the biosynthesis of cell walls to weaken interactions with host cells [135, 136]. Several reviews have been published describing the development of novel synthetic and natural product candidates as prototypes against *M. tuberculosis* and the possible biological targets of these candidates [137–139].

Drug candidates containing 1*H*-1,2,3-triazoles are relatively new, and there are no drugs or products in advanced clinical trials containing this moiety. The primary reason that these compounds have not been submitted to clinical trials is that the preparation of these heterocycles has been limited to a few synthetic methodologies, and these methods are unable to produce compounds with molecular diversity.

Interest in the 1*H*-1,2,3-triazoles in medicinal chemistry began to increase after the publication of the seminal work of Sharpless, who improved the Huisgen 1,3-cycloaddition reaction to selectively obtain the 1,4-disubstituted adduct of the 1*H*-1,2,3-triazoles using copper (I) as a catalyst [80–82, 107]. This cycloaddition reaction between an azide and an alkyne occurs under mild conditions with high yields and is an example of “click chemistry” [84]. A large number of original papers and reviews have been published describing Sharpless’ robust methodology in several solvents [88], as well as detailing combinatorial methods [92] and the mechanism of the reaction [93]. Subsequently, many new 1*H*-1,2,3-triazoles have been synthesized and widely exploited for their biological activities [94, 140, 141]. These triazoles are also able to display several bioactivity properties against several targets when the triazole is properly functionalized [84, 106, 107]. The 1*H*-1,2,3-triazoles have an appealing structural motif and electronic characteristics similar to those of a peptide bond (for peptidomimetic research) [98, 99]. In

**Fig. 6** General structures of 1,4- and 1,5-isomers of 1*H*-1,2,3-triazoles**Fig. 7** *N*-Alkyl- and *N*-aryl-1,4- disubstituted of the 1*H*-1,2,3-triazoles with anti-TB activity

addition, their ability to participate in hydrogen bonding and dipole interactions may favor binding to biomolecular targets and improve their solubility [102, 103].

The 1*H*-1,2,3-triazoles have been screened against several strains of *M. tuberculosis*, and some of them are candidates for antitubercular treatment [37]. In the disubstituted 1*H*-1,2,3-triazole series, it is possible to have two isomers, the 1,4- and 1,5-disubstituted isomers. Preparation of 1,4-disubstituted 1*H*-1,2,3-triazoles is easier than that of 1,5-disubstituted 1*H*-1,2,3-triazoles. Therefore, there are many more studies involving the synthesis and antitubercular activity of the 1,4-isomers than the 1,5-isomers (Fig. 6).

N-Alkyl- and *N*-aryl-1,4-isomers of the 1*H*-1,2,3-triazoles have been reported to have antimycobacterial activity. Gallardo et al. [142] found that compound **40** has a minimal inhibitory concentration (MIC) against *M. tuberculosis* H37Rv and ATCC 27294 of 3.1 $\mu\text{g/mL}$, indicating that a large series of this compound could be expanded, and its activity can be improved (Fig. 7). Following this lead, Boechat and coworkers prepared a large series (**41**) of 4-substituted *N*-phenyl-1*H*-1,2,3-triazole derivatives (Fig. 7) [37]. The basic structure of the triazoles was modified at positions 1 and 4 on the ring with various functional groups. In addition, from the aldehyde series, Boechat and coworkers prepared several new compounds containing the isoniazid (**42**) structural unit, which is a drug that is active against *M. tuberculosis* (MIC 0.002–0.006 $\mu\text{g/mL}$) and inhibits the synthesis of mycolic acids, which are

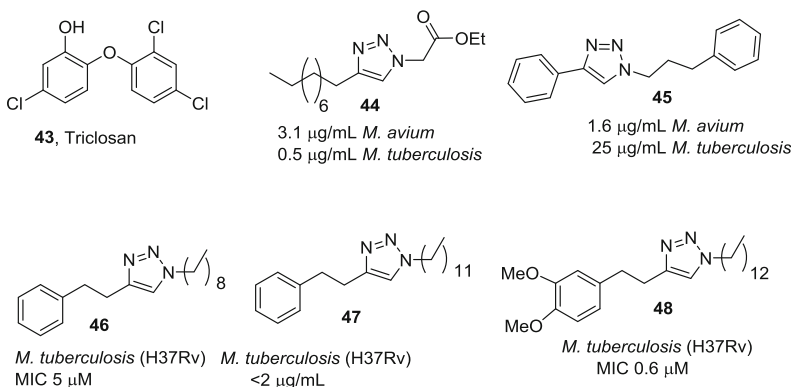
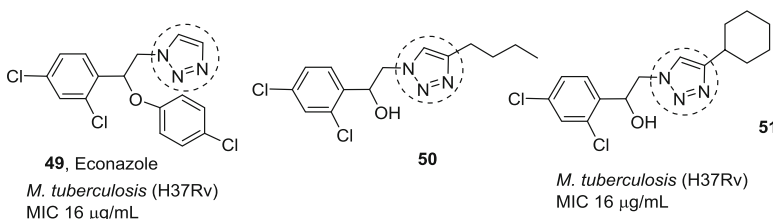
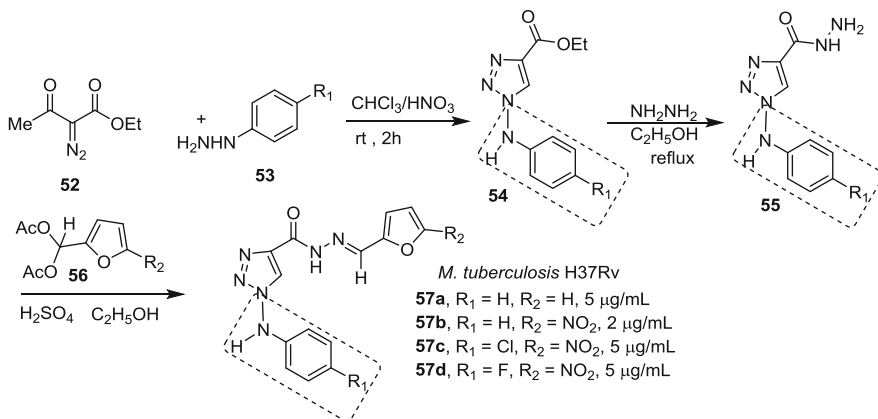


Fig. 8 Triazoles used for anti-TB targeting of 2-*trans*-enoyl-ACP reductase

components of the cell wall. This synthetic strategy has also been used by other research groups [143–145]. The substituents at the 4-position showed a more significant inhibitory activity than substituents at other positions. The reactivity order of the compounds having substituents at the 4-position on the triazole was the following: vinyl > CHO > CHF₂ > CF₃ > CH₂F > COOCH₃ > CH₂OH. Derivatives of isoniazid (**1**), (*E*)-*N'*-[(1-aryl)-1*H*-1,2,3-triazole-4-yl)methylene] isonicotinoyl hydrazides exhibited significant activity, with MIC values ranging from 2.5 to 0.62 μ M. In addition, these derivatives displayed low cytotoxicity against liver cells (hepatoma HepG2) and kidney cells (BGM), thereby exhibiting a high therapeutic index.

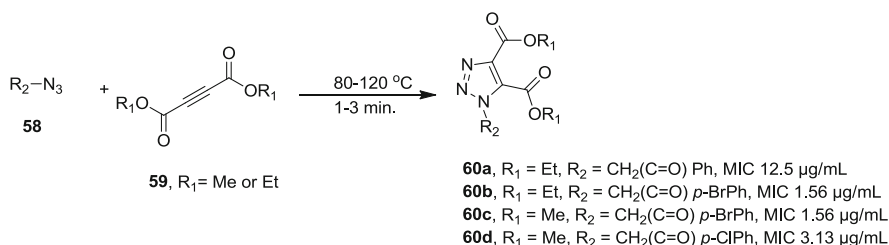
The acyl carrier protein 2-*trans*-Enoyl-ACP reductase is an important enzyme for the growth of *M. tuberculosis* sp. [146] because it is involved in mycolic acid biosynthesis. Thus, this enzyme is an important target for drugs to inhibit these bacteria. The drug triclosan (**43**) has been shown to significantly inhibit InhA' [147] which is also the primary target of isoniazid (**32**), a leading drug used to treat tuberculosis. Menendez et al. synthesized and tested several 1*H*-1,2,3-*N*-alkyl-triazoles for the inhibition of InhA in *M. tuberculosis* H37Rv and found good inhibitors of *M. tuberculosis* but weak inhibitors of InhA [148]. Certain compounds showed good activity toward *M. tuberculosis* with minimum inhibitory concentrations ranging from 2.0 to 5.0 μ g/mL. In the same year, Labadie and coworkers [149] prepared a small library of 1*H*-1,2,3-*N*-alkyl-triazoles, which could mimic the phenol central core of triclosan, and tested them against two strains of mycobacteria, *M. avium* and *M. tuberculosis*. More recently, Menendez et al. [150] continued their previous work and synthesized novel triazoles. Compounds possessing a methylene group (**41–48**) between the aromatic group and the triazole core inhibited *M. tuberculosis* H37Rv at 5 μ g/mL or higher. Note that the length of the alkyl chain attached to the triazole core does not significantly influence the activities, but in general, the length of the alkyl chain is important (Fig. 8). The best results were obtained for the 12-carbon chain derivatives (e.g., **48**, which shows an MIC value of 0.6 μ M).

Modification of antimicrobial agents sold in the pharmaceutical market is a strategy that has been used by several research groups. For example, the success

**Fig. 9** 1*H*-1,2,3-triazoles linked to the econazole framework**Scheme 4** NH linker with 1*H*-1,2,3-triazoles

of econazole (**49**) has encouraged the search for new analogs with antitubercular activity. Kim and coworkers explored the antitubercular activity of the 1*H*-1,2,3-triazoles linked to econazole and miconazole that have previously been successful in the treatment of multiple resistant TB (MDR-TB) and are active against *M. tuberculosis* CYP130 [151]. Two compounds, **50** and **51**, were promising because they were more active than econazole (**49**) and another compound that was equally active, indicating that the imidazole moiety of econazole can be replaced by the 1*H*-1,2,3-triazole core with the retention of the antitubercular activity (Fig. 9) [151, 152].

Cunha and coworkers studied substitution of the radical N-alkyl by an amino-sulfonic group. Their group synthesized several 1*H*-1,2,3-triazoles with a nitrogen atom as the linker between the heterocyclic ring and the aryl group [38]. Triazoles **54** were obtained in good yields by reacting α,α -dicarbonyl compounds, such as ethyl diazoacetate (**52**), with suitably substituted hydrazines (**53**). The triazoles obtained in this reaction were transformed into hydrazides (**55**), which were then coupled with various aldehydes or acetals. The triazoles **57a-d** showed activity against *M. tuberculosis* H37Rv, with MIC values ranging from 2.0 to 5.0 µg/mL. The best compound of this series was the triazole **57b**, which presented a MIC of 2.0 µg/mL (Scheme 4).

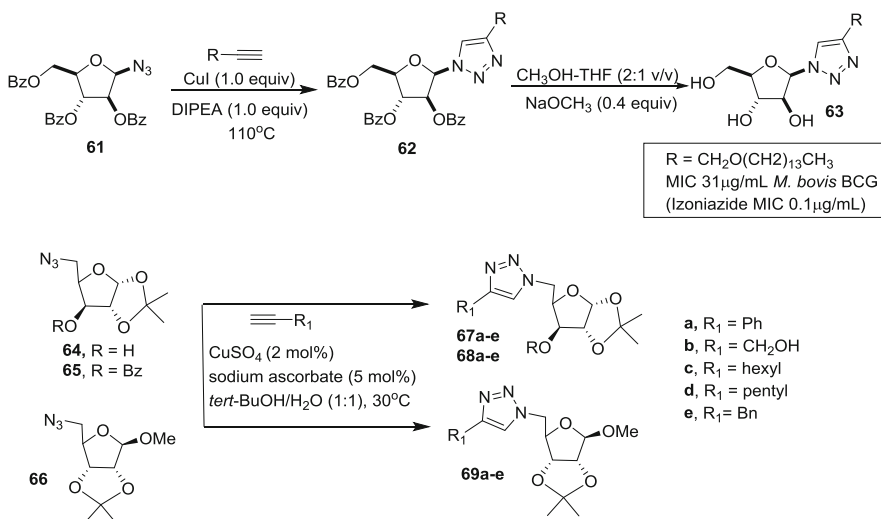


Scheme 5 Preparation of antitubercular 1,4,5-trisubstituted 1H-1,2,3-triazoles

Only a few examples of 1,4,5-trisubstituted 1H-1,2,3-triazoles have been synthesized and evaluated as antitubercular agents. Shanmugavelan et al. prepared several 1,4,5-trisubstituted 1H-1,2,3-triazoles (**60a–d**) in good yields using the classical Huisgen cycloaddition between alkyl or aryl azides (**58**) and diethyl or dimethyl acetylenedicarboxylate (**59**). The novelty of this methodology is the use of solvent-free reaction conditions, which is consistent with the principles of green chemistry. The compounds were tested against *M. tuberculosis* (H37Rv), and they presented moderate MIC values in the range of 1.56–3.13 $\mu\text{g/mL}$. The compounds **60b** and **60c** showed MIC values of 1.56 $\mu\text{g/mL}$, which is 2.08 times more active than the standard drug ethambutol (MIC 3.25 $\mu\text{g/mL}$) but less potent than the standard drug isoniazid (MIC 0.75 $\mu\text{g/mL}$) (Scheme 5) [153].

Lipids and polysaccharides containing mycolic acids, arabinogalactan, and peptidoglycan are abundant in the cell wall of mycobacteria. Because the mycolyl-arabinogalactan-peptidoglycan complexes are important for the bacteria, inhibition of their biosynthesis will affect the growth of these microorganisms [154]. Indeed, there are several drugs on the market used for the treatment of TB that target the mycobacterial cell-wall biosynthesis (e.g., thiacetazone, isoniazid, ethambutol, pyrazinamide, and ethionamide). Biomass-based carbohydrates are the most abundant natural products and have been used to develop technologies for the generation of chain products, such as fuels, chemical intermediates, and derivatives for the fine chemical industry. Glycoconjugates have a carbohydrate moiety and are involved in important biological functions, including those on the cell surface, such as the recognition of host compounds, immunological responses, inflammation, cell-cell recognition, bacterial and viral infection, cell communication, metastasis, and many important functions inside cells. Synthesis of triazole-tethered carbohydrates [155] or nucleosides represents a significant therapeutic opportunity for the development of new anti-tubercular agents.

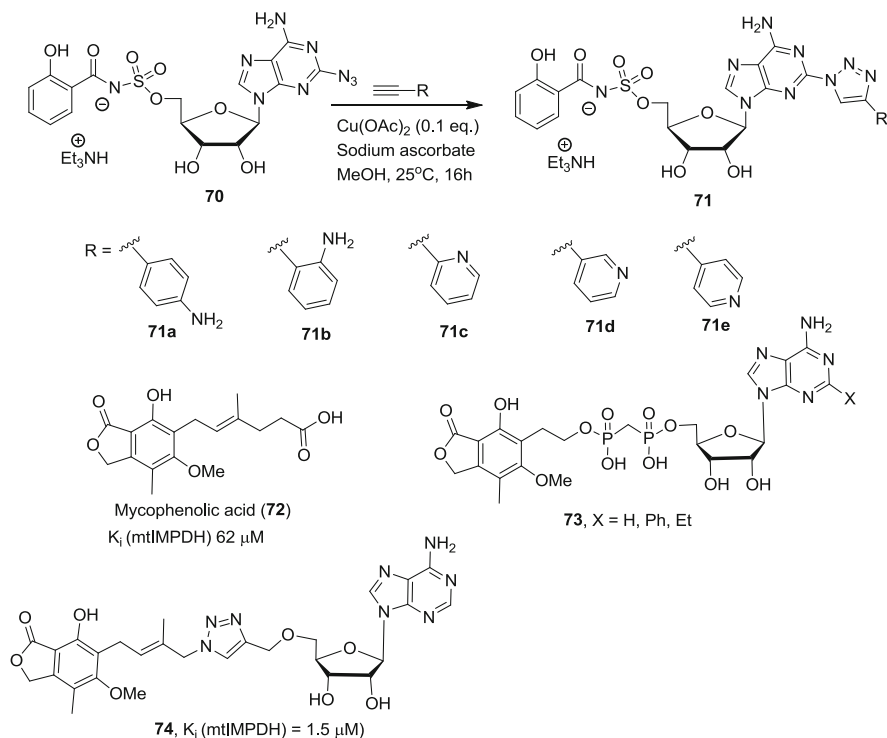
Fairbanks and his research group have focused on the discovery of arabinosyl transferase inhibitors [156], and using **61**, they synthesized a series of arabinoglycosyl triazoles with hydrophobic ligands as potential inhibitors of decaprenol-phosphoarabinose, thus targeting the biosynthesis of the mycobacterial cell wall. The compounds were tested against *Mycobacterium bovis* BCG (bovine tuberculosis), and the best result was obtained for **63**, which presented moderate



Scheme 6 Synthesis of carbohydrate-based 1*H*-1,2,3-triazoles

antitubercular activity at a concentration of 31 $\mu\text{g/mL}$, indicating that activity is strongly dependent on the hydrophobic side chain [156]. Similarly, Singh and coworkers have synthesized 1,2,3-triazoles linked to xylose acetonide by reacting 5-azido-5-deoxy-1,2-*O*-isopropylidene- α -D-xylofuranose (**64** or **65**) with several alkynes (Scheme 6) [157]. Likewise, 5-azido-3-*O*-benzyl-5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (**66**) was reacted with different alkynes. All of the obtained compounds (**67**, **68** and **69**) showed moderate MIC values against *M. tuberculosis* (H37Rv) of only 12.5 $\mu\text{g/mL}$ ($R=\text{OH}$ and $R_1=\text{H}$), whereas the MIC values for isoniazid (**28**, 0.65 $\mu\text{g/mL}$), rifampicin (**31**, 0.75 $\mu\text{g/mL}$), and ethambutol (**30**, 3.25 $\mu\text{g/mL}$) were much lower.

Nucleosides tethered to the triazole nucleus have been explored as potential drugs, and some of them have become pharmaceuticals (e.g., Ribavirin). Gupte and coworkers [158] synthesized several nucleosides with the core triazole moiety linked to an adenosine, resulting in new compounds with excellent activity against *M. tuberculosis* H37Rv. The 5'-*O*-[*N*-(salicyl) sulfamoyl] adenosine series is shown in Scheme 7. Compounds **71a–71e** showed very low MIC values (0.78 $\mu\text{g/mL}$). Another approach was used by Pankiewicz and co-workers [159] in which new compounds were designed to act on inosine monophosphate dehydrogenase (IMPDH), which is a key NAD-dependent enzyme that converts inosine monophosphate to xanthosine monophosphate. Inhibition of IMPDH depletes the supply of guanine nucleotides that are required for the growth and proliferation of cells, viruses, and bacteria [159]. In the strategy used by Pankiewicz, the structure of mycophenolic acid (**72**, Scheme 7), a known immunosuppressant drug used to prevent rejection in organ transplantation (CellCept or Myfortic), which inhibits

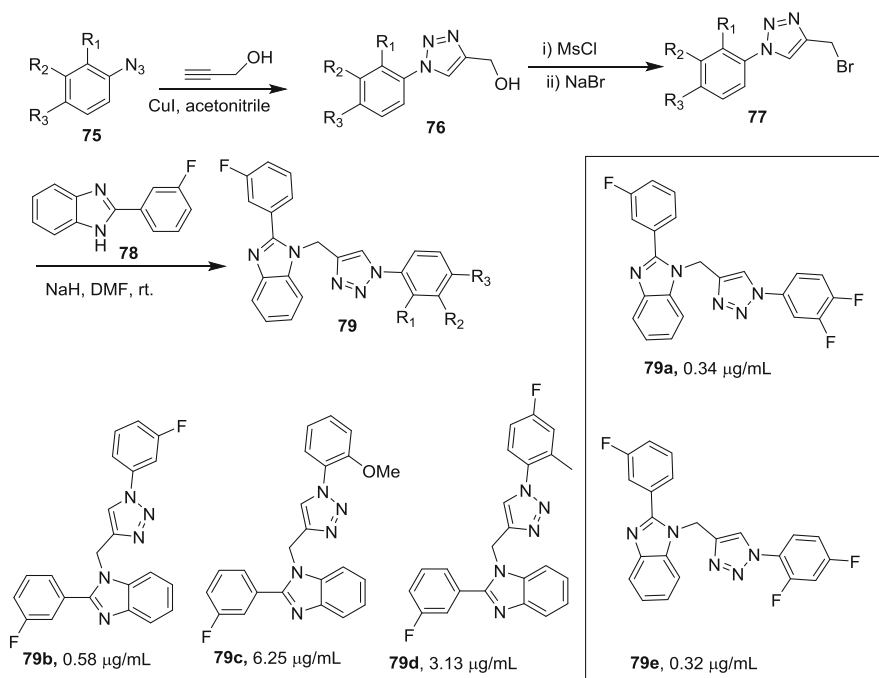


Scheme 7 Synthesis and antitubercular evaluation of triazoles linked with nucleosides

IMPDH by binding at its *N*-subsite, is joined with dinucleotide analogues of NAD. The NAD analogues interact with the subsites of the NAD cofactor-binding domain [160], which is present in the methylenebis(phosphonate) analogues of mycophenolic adenine (**74**), for which potential differentiation agents against human leukemia was found [161]. The NAD-mimicking inhibitors of IMPDH in which 1,2,3-triazole linkers replaced the pyrophosphate linker maintained the overall geometry and position of the mycophenolic moiety within the binding site of *M. tuberculosis* IMPDH (mtIMPDH). Evaluation of these inhibitors led to the identification of a low micromolar inhibitor (**74**, $K_i = 1.5 \mu\text{M}$) of human IMPDH and, more importantly, the first potent inhibitor of mtIMPDH [162]. It is possible that other analogues with different linkers would also enhance the selectivity against mtIMPDH.

Nitrogenated heterocycles typically present some type of biological activity. In view of this observation, the combination of different heterocycles has been a good strategy to discover new lead compounds in medicinal chemistry.

Gill and coworkers [163] prepared a group of imidazoles linked to triazole rings using 4-bromomethyl-1-phenyl-1*H*-1,2,3-triazole (**77**) as the coupling reagent with the imidazole (**78**). Several compounds (**79a–e**) were synthesized and two of those

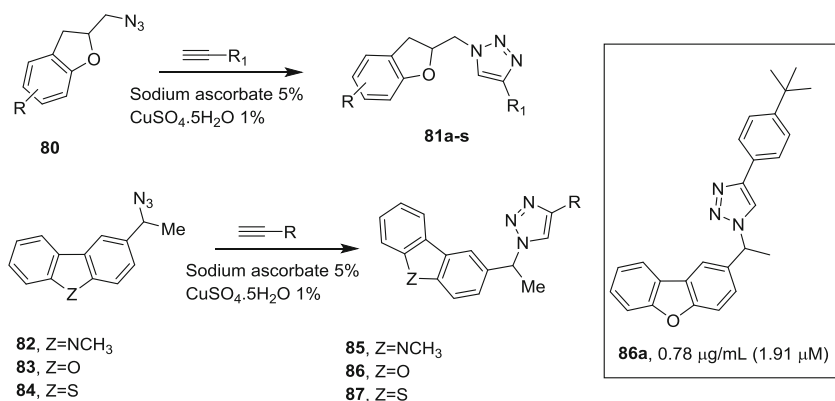


Scheme 8 Antitubercular triazole compounds tethered to an imidazole nucleus

compounds displayed excellent biological activities (**79a** and **79e**) against *M. tuberculosis* with MIC values ranging between 0.32 $\mu\text{g/mL}$ and 0.58 $\mu\text{g/mL}$ (Scheme 8). Botta and coworkers have also synthesized 1*H*-1,2,3-triazoles tethered to imidazole rings, but their compound showed a modest MIC value against *M. tuberculosis* H37Rv (ATCC 27294) [164].

A series of 1*H*-1,2,3-triazoles linked to dihydro-benzofuran were synthesized in good yields (59–94%) via a click reaction with 2-(azidomethyl)-benzofurans (**80**) (Scheme 9) [165]. These compounds were tested against *M. tuberculosis* H37Rv and were found to have MIC values between 3.12 and 5.12 mg/mL . Similarly, Patpi and coworkers have synthesized three series of 1*H*-1,2,3-triazoles linked to benzofuran and benzothiophene 9*H*-carbazole in excellent yields (82–96%). Evaluations against *M. tuberculosis* H37Rv (ATCC 27294 Strain) indicated that the MIC values were superior to those for ethambutol (**34**) and pyrazinamide (**33**) (Scheme 9) [166].

The quinoline or 1-azanaphthalene moiety is a structural feature present in many natural products and synthetic compounds that have become drugs in the therapeutic arsenal, especially as anticancer, antimalarial, and antimicrobial compounds [167–169]. Quinoline tethered to a triazole nucleus has also demonstrated potential bioactivity [170]. Promising activities have been shown by 4-(adamant-1-yl)-2-quinolinecarbohydrazide (**88**) and its analogues [171] against drug-sensitive and



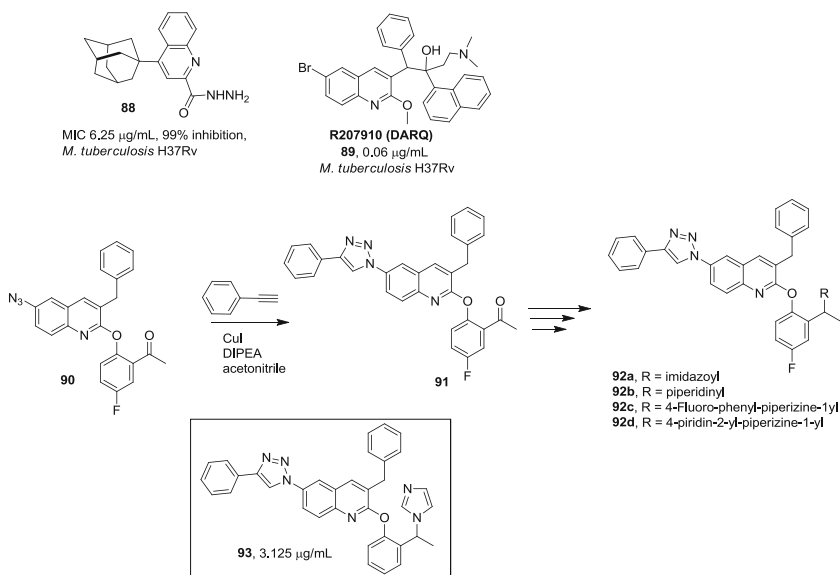
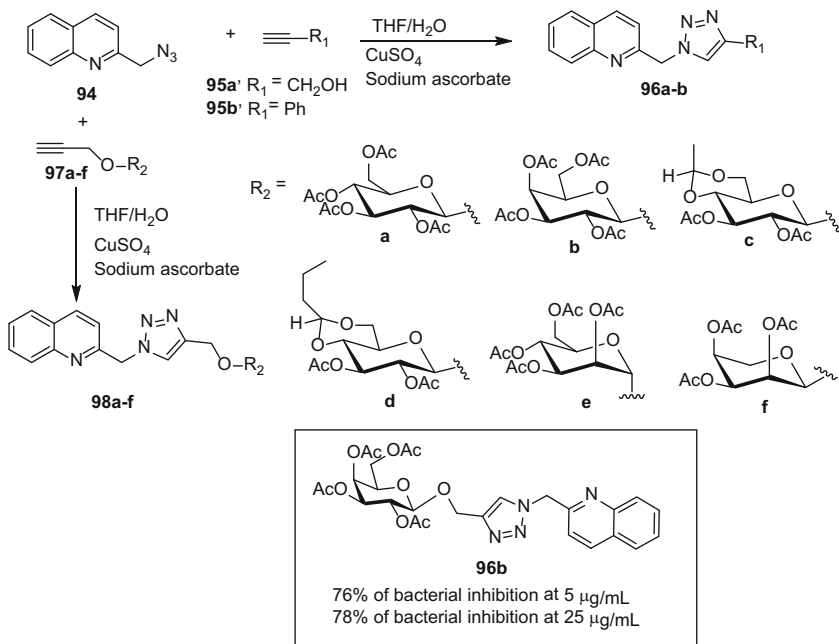
Scheme 9 Triazoles linked to dihydro-benzofurans, dibenzothiophenes and 9H-carbazoles

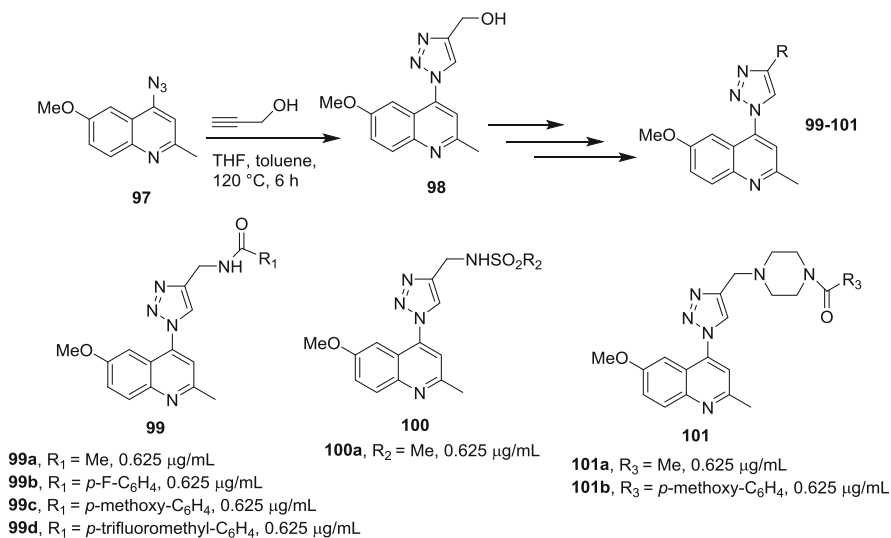
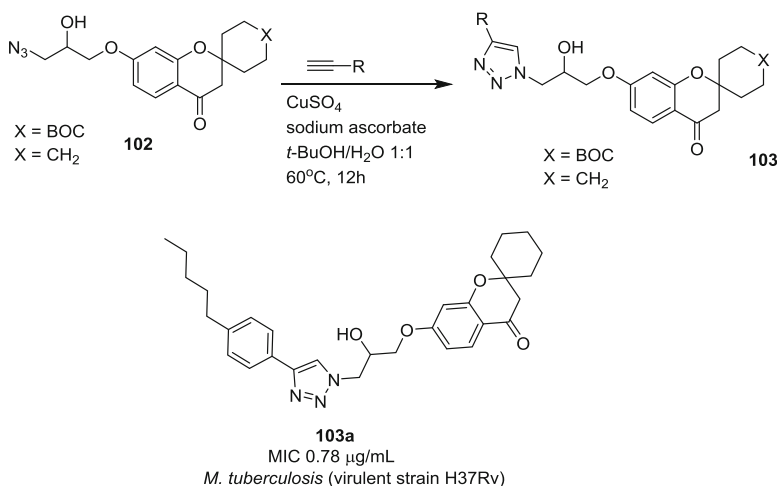
resistant *M. tuberculosis* H37Rv strains [172]. In addition, diarylquinolines (DARQs, e.g., **89**) have demonstrated potent anti-mycobacterial activity against replicating bacilli both in vitro and in vivo, which has resulted in compound R207910 [173–175] that selectively inhibits the ATP synthase proton pump of both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* with an MIC value of 0.06 µg/mL [131]. Therefore, Upadhyaya and coworkers [175] have synthesized a series of 20 quinoline derivatives possessing triazolo, ureido, and thioureido substituents. All of the compounds were evaluated against *M. tuberculosis*, but only one compound (**93**, R=imidazolyl) showed good results, with a 96% growth inhibition of *M. tuberculosis* H37Rv and a minimum inhibitory concentration of 3.125 µg/mL (Scheme 10).

Kumar et al. used the same strategy and coupled the triazole nucleus at position 2 of the quinolinic ring (**96a–s** in Scheme 12) [176]. The triazole-quinoline derivative **96b** showed the best result, inhibiting bacterial growth by 76% and 78% at concentrations of 5 µg/mL and 25 µg/mL, respectively (Scheme 11).

Thomas et al. synthesized a series of 1H-1,2,3-triazoles attached to position 4 of the quinoline nucleus (**99–101**) [177]. These substances were tested against *M. tuberculosis* H37Rv and displayed excellent results with a minimum inhibitory concentration of 0.625 µg/mL; the MIC values obtained for **35** (rifampicin) and **32** (isoniazid) were 0.5 and 0.7 µg/mL, respectively (Scheme 12). β-lactam-ferrocene-triazole conjugate triazoles were prepared and tested against *M. tuberculosis* mc²7000 using cephalexin, a β-lactam antimicrobial, as a positive control (MIC value of 10–25 µg/mL), but even at high doses, they failed to inhibit growth [178].

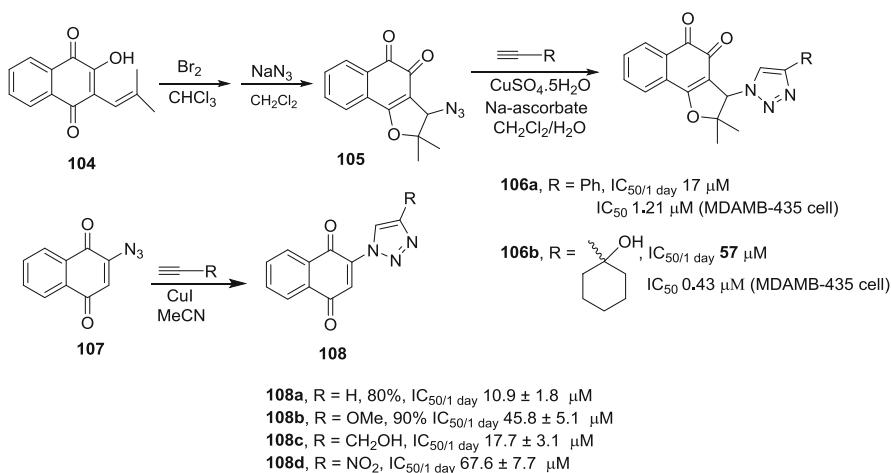
Several triazole compounds linked to a spirochromone were synthesized by Muthukrishnan and coworkers [179], and their MIC values ranged from 0.78 to 25 µg/mL. The compound **103a** was the most active of the series against *M. tuberculosis* H37Rv (ATCC27294) (Scheme 13).

**Scheme 10** Synthesis of antitubercular triazoles tethered to quinoline rings**Scheme 11** Antitubercular triazoles linked at the 2-position of quinoline

**Scheme 12** 1H-1,2,3-triazoles linked at position 4 of the quinoline**Scheme 13** Triazole-spirochromone conjugates as antitubercular agents

4 *Trypanosoma cruzi*

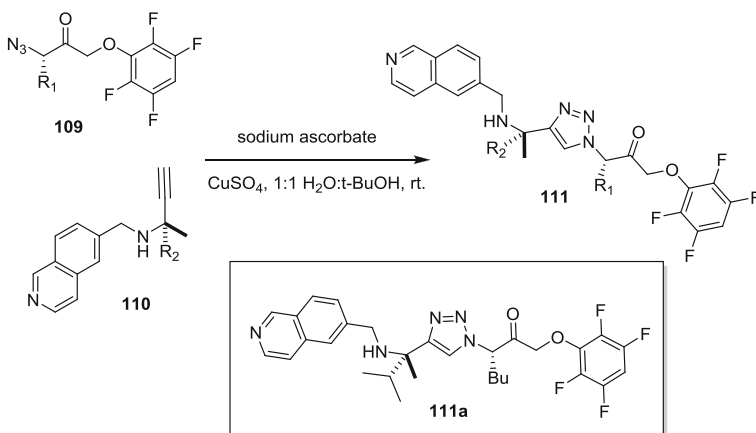
Quinones are natural products present in various families of plants, fungi bacteria, and insects linking the electron transport chains in the metabolic pathway with the oxidative processes. Because of these properties, over the past few years, several series of synthetic substances have been investigated as prototype bioactive



Scheme 14 Trypanocidal compounds obtained by molecular hybridization of naphthoquinone and 1,2,3-1*H*-triazole moieties

compounds to be used to treat several diseases. Certain compounds of this class have become pharmaceuticals and others have remained prototypes. This fact can be demonstrated by the large number of publications exploring the actions of these substances in various biological functions [180–182]. Briefly, quinones have been studied for antitumor [183, 184], molluscicidal [185–187], leishmanicidal [188], anti-inflammatory [189], antifungal [190], and trypanocidal [191, 192] activities. Regarding the trypanocidal agents, Chagas' disease is an enormous public health problem caused by the parasite *T. cruzi* that is endemic in Latin America and transmitted by triatomine insects while blood feeding on a human host.

Ferreira and coworkers, for the first time, incorporated a triazole ring to a naphthoquinone framework and assayed them against the infective bloodstream trypomastigote form of *T. cruzi* [193]. All of the derivatives were more active than the original quinones, with IC_{50/1 day} values in the range of 17–57 μM . The two most active compounds were substituted triazoles **106a** and **106b** (Scheme 14). This series of triazole-naphthoquinones emerged as interesting new lead compounds in drug development for Chagas' disease. Note that these furonaphthoquinone-1,2,3-triazoles also have potential clinical utility in the treatment of human cancer. These compounds have had their cytotoxic activities evaluated against the following six neoplastic cancer cell lines: SF-295 (central nervous system), HCT-8 (colon), MDAMB-435 (melanoma), HL-60 (leukemia), PC-3 (prostate), and B-16 (murine melanoma) and against one normal cell, the murine fibroblast L-929. The same triazoles **106a** and **106b** showed high and selective activity against melanoma cell line MDAMB-435 (Scheme 14) [45]. Similar molecular hybridization of furonaphthoquinone linked to 1,2,3-triazole was extended for the synthesis of a 1,4-naphthoquinone linker to 1,2,3-triazole (**108a–d**) and tested against *T. cruzi* trypomastigote forms. The authors [194] also observed

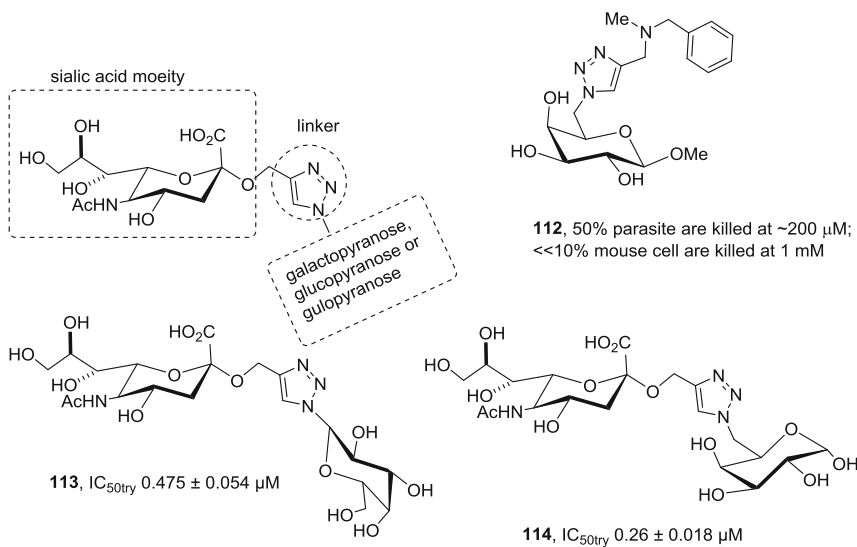


Scheme 15 Triazoles as nonpeptidic inhibitors of cruzain

that insertion of a 1,2,3-1H-triazole moiety into 1,4-naphthoquinone enhanced its trypanocidal activity (Scheme 14).

Ellman and co-workers prepared by regioselective Cu(I)-catalyzed 1,3-dipolar cycloaddition a series of 1,2,3-1H-triazole tetrafluorophenoxy (**111**) compounds to be tested as nonpeptidic inhibitors against the key enzyme cruzain from *T. cruzi* (Scheme 15) [195, 196]. The triazole **111a** was found to be an irreversible inhibitor that completely eradicated the *T. cruzi* parasite in cell culture (Scheme 15). The mode of inhibition and the binding interactions of **111a** were revealed by the high-resolution X-ray structure of the co-crystal with cruzain. Treatment of mice infected with *T. cruzi* parasites (trypomastigotes) for 27 days with **111a** substantially improved the symptoms of acute Chagas' disease with no apparent toxicity.

The trans-sialidase from *T. cruzi* (TcTS) is a unique glycosyltransferase enzyme involved in mammalian host-cell invasion by transferring sialic acids from glycoconjugates of the host to the terminal β -galactopyranosyl units present on the surface of the parasite [197, 198]. Thus, this enzyme is an important target for preparing new compounds that can inhibit its action and, consequently, the growth of *T. cruzi* [199]. To date, there are several synthetic and natural compounds that have been classified as inhibitors of TcTS [199–201]. Carvalho and coworkers, in an effort to find new inhibitors of this enzyme, prepared a series of 1,2,3-triazole galactosyl derivatives and sialylmimetic neoglycoconjugates for the evaluation against trypomastigote forms of the *T. cruzi* Y strain [202] and the *T. cruzi* Tulahuen strain [141], respectively. The *N*-methyl benzylamine derivative (**112**) was the best candidate of the galactosyl series, and the compounds **113** and **114** presented good inhibitory effects against the parasite in a nanomolar range, indicating that the 1,2,3-triazole ring is a good moiety for the design of trypanocidal compounds (Scheme 16).

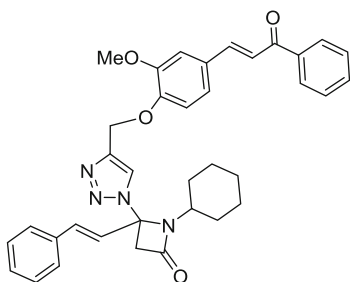
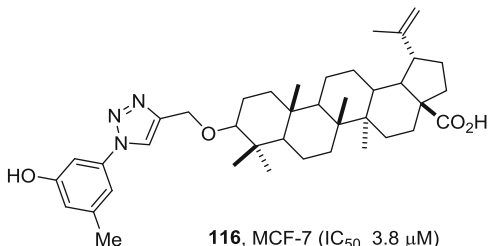
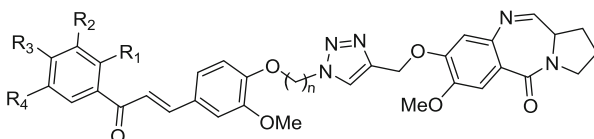
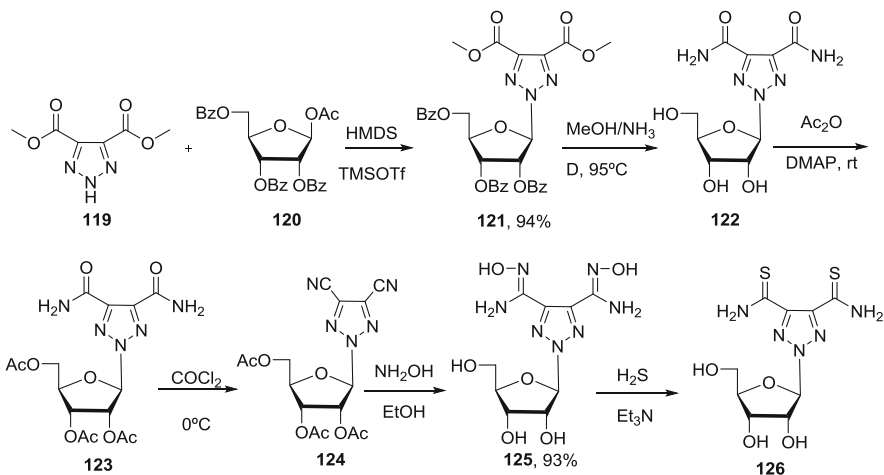


Scheme 16 1,2,3-triazole galactosyl sialylmimetic derivatives against *T. cruzi*

5 Anticancer Activity

The discovery of new drugs for cancer therapy is one of the medicinal chemistry's most investigated areas because the global prevalence of this disease continues to grow. The greatest challenge for scientists in this area is to develop new drugs that are more effective and have lower toxicity. Selectivity is the dilemma in cancer therapy for the achievement of drug delivery to a localized tumor and for an even distribution throughout the body, including the tumor tissues. Other challenges in the treatment of cancer using chemotherapy include drugs with short half-lives in blood circulation, fewer side effects, and effectiveness. The development of research in this area aims to attack the problem from different angles, such as chemotherapy conjugated with drug carriers to act as magic bullets or to enhance distribution of the drug molecule in the body [203].

Recently, several triazoles have been found to have activities against several cancer cell lines [83, 204, 205]. The researchers are focusing their efforts on the anticancer activity [206–208] in compound hybrids of 1,2,3-1*H*-triazole tethered with the β -lactam (**115**), triterpenoid (**116**), and chalcone (**117**, **118**) moieties that were evaluated against several cancer cell lines and were selective to A-549(lung) [209], chalcone-pyrrolo[2,1-*c*] [1,4]benzodiazepine conjugates containing alkane spacers with promising in vitro anticancer activity in concentrations ranging from <0.1–2.92 μM [210]. These compounds have also been screened on the apoptosis enzymes that regulate cellular programmed cell death of unnecessary cells as shown in Fig. 10 [211, 212].

**115**, A549 (93% inhibition at 50 μM)**116**, MCF-7 (IC_{50} 3.8 μM)**117**, $\text{R}_1 = \text{OH}$, $\text{R}_2, \text{R}_3, \text{R}_4 = \text{H}$; $n = 2$, MCF-7 (IC_{50} 0.14 μM); A2780 (IC_{50} 0.10 μM)**118**, $\text{R}_1 = \text{OH}$, $\text{R}_2, \text{R}_3, \text{R}_4 = \text{H}$; $n = 3$, MCF-7 (IC_{50} 0.14 μM); A2780 (IC_{50} 0.14 μM)**Fig. 10** Examples of triazole linkers active against cancer cell lines**Scheme 17** 1,2,3-2H-triazole analogues of ribavirin

Drugs used therapeutically for other diseases can serve as models in the search for new lead compounds. Revankar and coworkers synthesized a series of six analogues of the antiviral drug ribavirin (**121–126**) containing 1,2,3-2H-triazoles and studied them as inhibitors of the tumor cell line HL-60 [213]. The derivatives were obtained by a synthetic sequence (Scheme 17) that begins with a condensation reaction between the triazole compound (**119**) and ribofuranoside (**120**) catalyzed

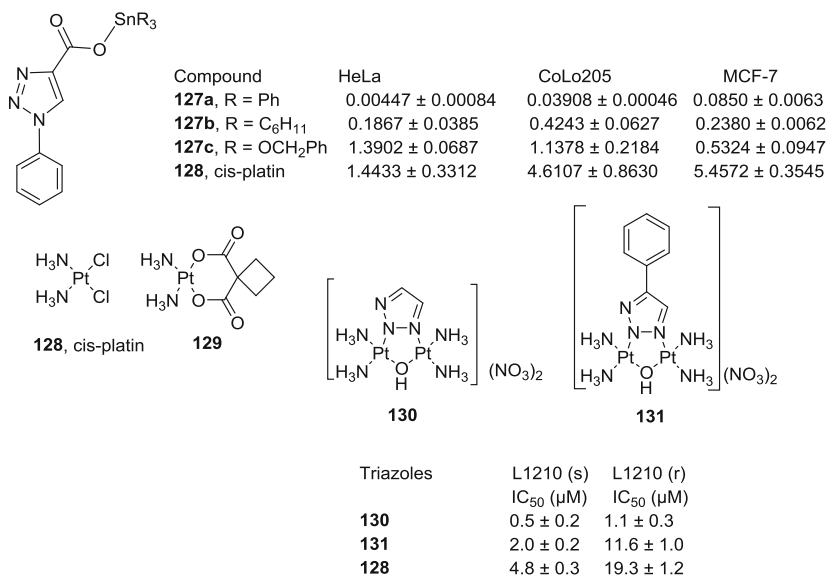
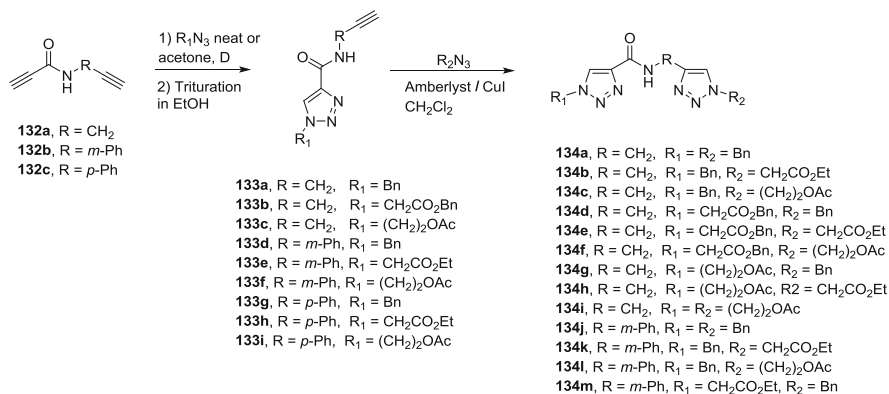


Fig. 11 Platinum complexes with triazoles and their activities in tumor cell lines

by a Lewis acid, trimethylsilyl triflate. The product **121** is then converted by several reactions to the nucleosides **122–126**. **126** inhibited HL-60 at a level that was 50% of the inhibitory effect of ribavirin (Scheme 17).

Metal complexes are widely used in chemistry and in many treatments of diseases, including cancer chemotherapy. For example, organotin (IV) carboxylates are used in many applications in chemistry and biology, such as antitumor activity [214]. Tiam and coworkers synthesized three triorganotin 2-phenyl-1,2,3-triazole-4-carboxylates (**127a–c**), and a bioassay showed that these compounds have good antitumor activity against three human tumor cell lines (HeLa, CoLo205, and MCF-7) [215]. In addition, platinum complexes are widely used in cancer chemotherapy. For example, cisplatin, approved by the FDA in 1978, and carboplatin [216], are the most commonly used anticancer platinum complexes in the clinical treatment of testicular and ovarian malignant tumors [217–219], and their mechanism of action is the induction of apoptosis [220, 221]. Considering these findings, Reedijk and coworkers [222] synthesized two binuclear platinum complexes [223] with triazoles as ligands. The compounds **130** and **131** demonstrated to have better anticancer activity (18 times more cytotoxic) than cisplatin against tumor cell lines (acute lymphoblastic leukemia cisplatin-sensitive and cisplatin-resistant) (Fig. 11).

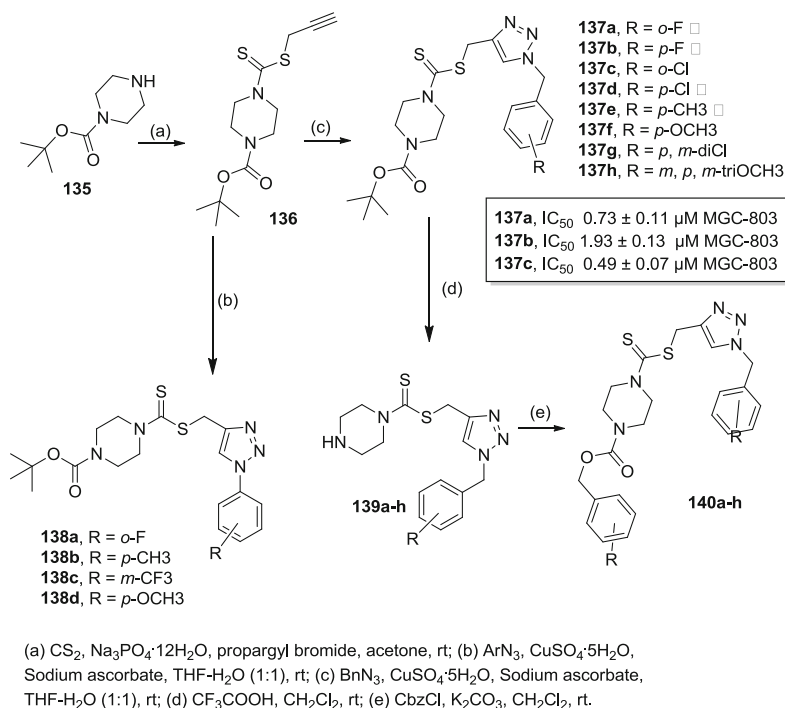
Girard and coworkers [224, 225] synthesized mono- and bis-1,2,3-triazoles from bis-alkynes to be tested against the human tumor strain B16 (murine melanoma cell line) that is highly malignant, metastatic, and chemoresistant [226–228]. The new compounds were obtained based on the previous experiments conducted by the group, which synthesized 1,4-disubstituted-1,2,3-triazole analogs of combretastatin



Scheme 18 Series of 1,4-disubstituted mono- and bis-1,2,3-triazoles with some cytotoxic activity in tumor strain B16

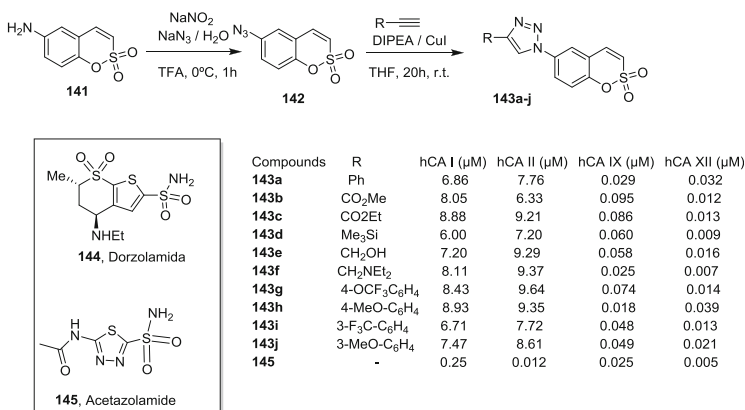
A-4 (a natural stilbenoid isolated from *Combretum caffrum*). All of the compounds, including their precursors, were tested in cultures of human melanoma cells B16. The presence of one triazole ring did not prove to lead to a good inhibitor; on the contrary, the alkyne precursors **133a** ($38.0 \pm 0.4 \mu M$), **133b** ($0.3 \pm 0.008 \mu M$), and **133c** ($6.3 \pm 0.3 \mu M$) were generally more active than the mono-substituted-1,2,3-triazoles **134a–i**. The bis-triazoles showed significant changes in the cytotoxicity. The derivatives **134a** ($0.3 \pm 0.003 \mu M$) and **134j** ($4.5 \pm 0.3 \mu M$) showed the most favorable results from this series (Scheme 18).

Dithiocarbamate derivatives are well known in the literature as fungicidal [229] and bactericidal [230] compounds, as well as inhibitors of carbonic anhydrase enzymes [231, 232]. Liu and coworkers [233–235] prepared 1,2,3-triazoles containing a dithiocarbamate pharmacophoric group and studied their antitumor activity [236–238]. The desired dithiocarbamate-alkynes were synthesized in a one-pot reaction using the carbamate **135**, CS_2 , and propargyl bromide. The appropriate dithiocarbamate-alkynes were reacted with azides via click chemistry to produce several series of dithiocarbamate-triazoles (**136**). The compounds were tested in cell lines of MGC-803 (gastric cancer), MCF-7 (breast cancer), PC-3 (human prostate cancer), and EC-109 (esophageal squamous cell carcinoma) using a 5-fluorouracil standard positive control (IC_{50} MGC-803 7.01 ± 1.34 ; MCF-7, 7.54 ± 0.7 ; PC-3 27.07 ± 4.21 ; EC-109 3.34 ± 0.86). The results of the inhibition of the growth of cells of all of the synthesized derivatives have shown that the compound **137a** is more cytotoxic than the positive control as an injectable or in topical applications [239]. In addition, compound **137c** showed good activity, 14 times more active than the positive control for the strain MGC-803 (gastric cancer), but was less active than the control only for strain EC-109 (esophageal cancer). Removal of the tertiary butyl oxycarbonyl group (series **139a–h**) generates a loss of activity and the introduction of the carbobenzoxy group (series **139a–h**) (Scheme 19).



Scheme 19 Synthesis and anticancer activities of 1,2,3-triazole-dithiocarbamates

Human carbonic anhydrase (hCA) is a metalloenzyme with 15 isoforms [240] that are involved in various physiological processes [241], such as breathing, CO₂/bicarbonate transport between tissues and lungs [242], homeostasis, biosynthetic reactions, bone resorption, calcification, growth, and virulence of several pathogens [243] and tumorigenicity [244, 245]. The hCA isozymes IX and XII are overexpressed in cancer cells where they regulate a pH level that contributes to hypoxic tumor cell survival and proliferation. These enzymes are important for the growth of primary breast cancer tumors and metastasis [246]. Coumarins significantly inhibit carbonic anhydrase [247–250]. Coumarin bioisosteres, sulfocoumarins, also target human carbonic anhydrase-associated tumors, as reported by Supuran and coworkers [251–253]. Dorzolamide **144** (Trusopt) is an approved pharmaceutical drug that targets carboxylic anhydrase and is used in ophthalmic compositions for the treatment of ocular hypertension or glaucoma. The sulfohexyl moiety appears to be important for the activity of this compound. Recently, Zalubovskis and coworkers [254] prepared a facile synthetic protocol to prepare a series bioisosteres in which the carbonyl group is replaced by a sulfonyl group (Scheme 20). The synthesis begins with the diazotization of the sulfocoumarin **141**, which is transformed into an azide and then reacted with various alkynes to form the triazoles **143a–j** by 1,3-dipolar cycloaddition. These triazoles have shown inhibitory activity in both hCA I and II enzymes and for hCA



Scheme 20 Synthesis of 1,2,3-triazole-sulfocoumarins

IX and XII enzymes, which are related malignant tumors in nanomolar concentrations. The derivative **143b** showed the best inhibitory activity for hCA IX, and **143c** was 11 times more potent than acetazolamide **145** (a carbonic anhydrase inhibitor for the treatment of glaucoma, epileptic seizures, etc.), which was used as a positive control.

Metal complexes are widely used as pharmaceuticals in several diseases, including cancer treatment. Further attention has been focused on the iron complexes, ferrocenes, because they can be administered orally and have very low toxicity. Therefore, ferrocene-based compounds have been used in several therapies. Poulsen et al. [255] planned the synthesis of 1,2,3-triazoles tethered (**146–153**) with a phenyl sulfonamide (PhSO₂NH₂) tail, a recognized pharmacophore that inhibits hCA enzymes, and with a head composed of a ferrocene (iron) or ruthenocene (ruthenium) complexes that also affect the hCA enzyme. Compound **151** from this series was the most potent ferrocene-based inhibitor with a K_i value of 5.9 and 6.8 nM for hCA IX and XII, respectively (Fig. 12).

6 Diabetes Mellitus

A glycosidic bond, consisting of α - or β -linkages at the anomeric center, is a covalent chemical bond that joins two simple sugars using an oxygen atom. Many polysaccharides are formed by joining monosaccharides by α - or β -glycosidic bonds. During the digestion process, these bonds are hydrolyzed by specific glycosidase enzymes, liberating the carbohydrate units as nutrients [256]. For example, the amylase enzymes are produced in the digestive system to break down the α -glycosidic bonds of starch. There are several enzymes that control carbohydrate usage as nutrients. Peroxisome proliferator-activated receptor (PPAR) agonists have the ability to improve glucose tolerance in type 2 diabetic

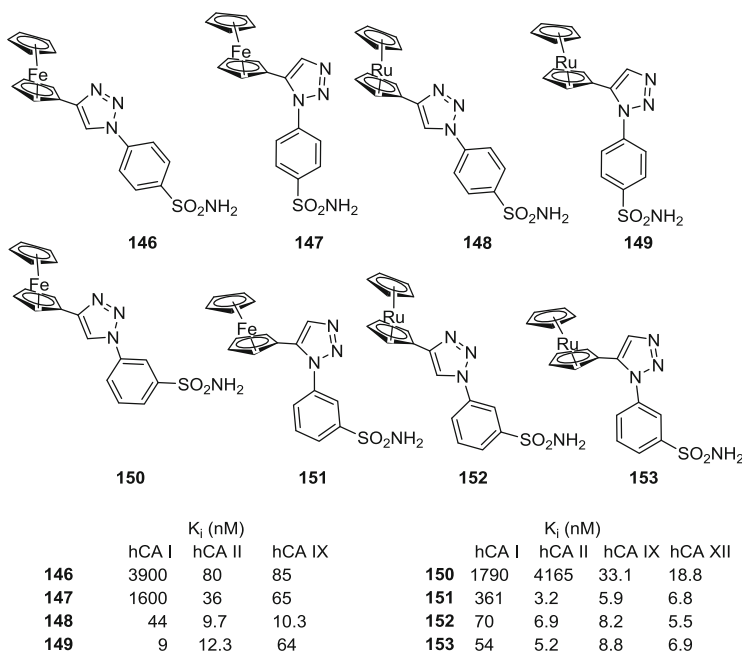
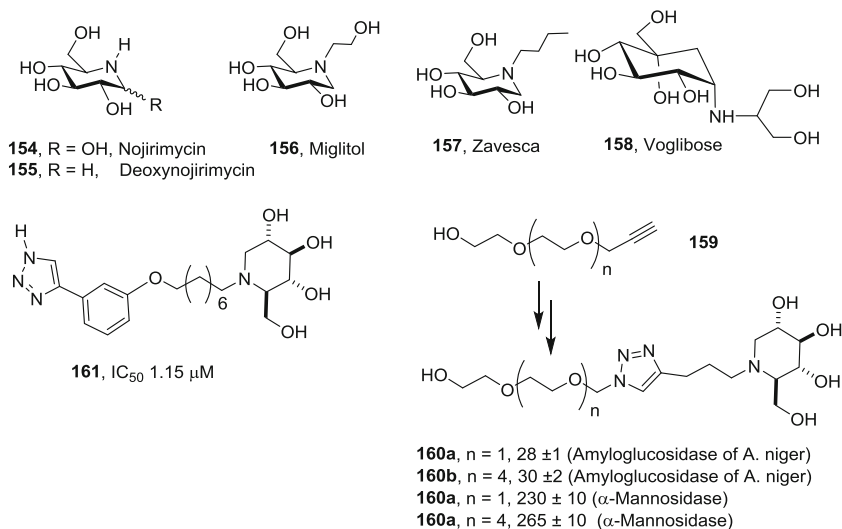


Fig. 12 Ferrocene- and ruthenocene-based compounds tethered to 1,2,3-triazoles

patients [257] and improve the regulation of glycosidase enzymes. The latter enzymes are involved in important biological processes, such as intestinal digestion and lysosomal catabolism of glycoconjugates. The inhibitors are designed to act as antagonists of α - and β -glucosidase enzymes, interfering with the digestion of carbohydrates and slowing the rate of absorption of monosaccharides, resulting in decreased levels of blood glucose. In addition, the PPAR agonists are useful as antiviral agents [258, 259], anti-cancer metastasis [260], against obesity, genetic diseases, and as anti-diabetic agents. Therefore, inhibition of digestive α - and β -glucosidases could be used therapeutically for the treatment of metabolic diseases, such as diabetes mellitus, which is a chronic metabolic disorder characterized by hyperglycemia (an abnormal increase in blood glucose from insufficient secretion and insulin action).

Many organisms have endogenous inhibitors that regulate the activity of their glycosidases and glycosyl transferases. Nojirimycin (**154**) and deoxynojirimycin (**155**, 1-DNJ) are two classical iminosugars [261, 262] glycosidase inhibitors that act in the early stages of glycoprotein processing and are isolated from plants or the cultured broth of the *Streptomyces* species. Nojirimycin (**154**) was the first natural piperidine heterocycle that mimicked D-glucose with a nitrogen atom in place of the ring oxygen with potent inhibition activity for α - and β -glucosidases from various sources. These natural iminosugar products have served as a model for the design and synthesis of tethered or fused [263] compounds that incorporate their



Scheme 21 Examples of hybrid iminosugars based on 1-DNJ inhibitors of glycosidases

most important structural features [264, 265]. Currently, the following three drugs are used therapeutically in the treatment of non-insulin-dependent diabetes as anti-glucosidases: 1-(2-hydroxyethyl)-2-(hydroxymethyl)-1-deoxynojirimycin (**156**, Miglitol or Glyset) [266], *N*-butyl-1-deoxynojirimycin (**157**, Zavesca) and voglibose (**158**, Vogli, Basen, or Prandial) (Scheme 21). New compounds with inhibitory activity on glycosidases led to the discovery that five-membered azaheterocycles mimic the sugar moieties; thus, various compounds containing the pyrrole, imidazole [267, 268], tetrazolo-glyco-derivatives, and [1,2,3]-1*H*-triazole [269–275] groups were prepared and evaluated. Because the alkyl chain linker of *N*-butyl-1-deoxynojirimycin (**157**) does not have a deleterious effect on the inhibition of α -glucosidases on glycosidase activity, Zhou and coworkers [276] designed and synthesized a series of triazoles linked to nojirimycin (**154**) and evaluated their ability to inhibit α -glucosidase from *Bacillus stearothermophilus*. The compound **161** shown in Scheme 21 was more active than nojirimycin (**154**, IC₅₀ 1.67 μ M). More recently, Kovensky et al. [277] reported the synthesis of several iminosugars using the click chemistry methodology between oligoethylene and the azide of *N*-substituted deoxynojirimycin. The compounds **160a** ($n = 1$) and **160b** ($n = 4$), which are derivatives of the 1-deoxynojirimycin compound, are moderate inhibitors toward different glycosidases (Scheme 21). The compounds of this series did not show better activity when tested against glycosidases compared with 1-deoxynojirimycin (**155**).

There is also considerable interest in designing molecules that are able to mimic the carbohydrate units and evaluating them against glucosidase enzymes [278]. The combination of both carbohydrate and 1,2,3-triazole structural units has proven to be useful for the production of new compounds with various biological activities

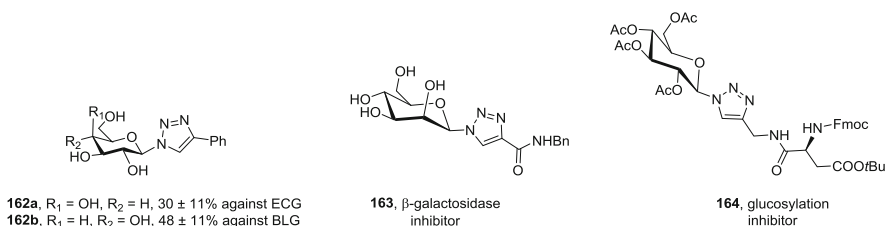


Fig. 13 Examples of glycotriazoles that mimic iminosugar inhibitors

[279–282]. One of the first examples of this approach was the synthesis [283] of glycosyl triazoles (**162a,b**) at the anomeric position followed by inhibitory evaluation against *Escherichia coli* galactosidase (ECG) and bovine liver galactosidase (BLG). These compounds showed the modest anti-glucosidase activity compared with nojirimycin (**154**) and deoxynojirimycin (**155**) [284]. Recently, the 1-glucopyranosyl 1,2,3-1*H*-triazole series was synthesized using improved methodology and with the introduction of halogens at position 5 of the triazole ring [285] (Fig. 13).

Several new glycosidase inhibitors have been isolated from plants and microorganisms [286]. A search for glycosidase inhibitors led to the discovery of acarbose (**165**) (Glucobay®, Precose), isolated from the *Actinoplanes* strain SE 50. This drug is a complex oligosaccharide for oral administration that is an inhibitor of α -glucosidase, which acts by delaying the digestion of carbohydrates ingested in the diet, thereby reducing the concentration of blood sugar after meals. Because of the reduction of blood glucose levels, there is a decrease in the glycosylated hemoglobin in patients with diabetes mellitus type II (non-insulin dependent). Following the previous pattern of introducing the triazoles ring into the structure's natural product, several compounds were synthesized and tested as glycosidase inhibitors [271]. Surprisingly, the mimetic triazole (**168**) did not improve the inhibitory activity. The compound with more carbohydrate units (**167**) did not show high activity, but the compound with only one glycol-triazole (**166**) with one carbohydrate unit was more active than acarbose against α -glucosidase and certain other glycosidases (Fig. 14).

Ferreira and coworkers [274] have synthesized a series of glycosyl triazoles (**169–172**) that have also demonstrated strong action as α -glucosidase inhibitors, and their bioactivity has been associated with their ability to mimic the charge buildup and/or the conformational distortion of the transition state thought to develop in the glycosidic bond during enzymatic cleavage. All of the compounds were initially screened for α -glucosidase inhibition at 500 μM , and the results revealed that most of them presented an inhibitory profile higher than that of acarbose (IC_{50} 108.8 ± 12.3 μM); notably, the ribosyl derivatives had the following IC_{50} values: **169b** (IC_{50} 3.8 ± 0.5 μM); **169e** (IC_{50} 5.7 ± 0.3 μM), and **169g** (IC_{50} 5.2 ± 0.9 μM). The pharmacological potential of this triazole series was demonstrated by the reduction of post-prandial blood glucose levels in normal rats treated with a 50 mg/kg oral dose of compounds **169a** or **169e**. This result

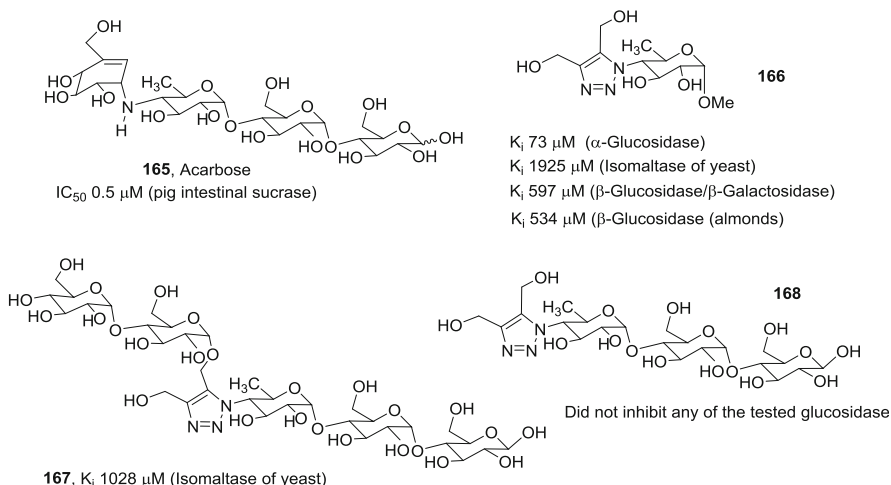


Fig. 14 Glycotriazoles that are structurally related to acarbose (**165**)

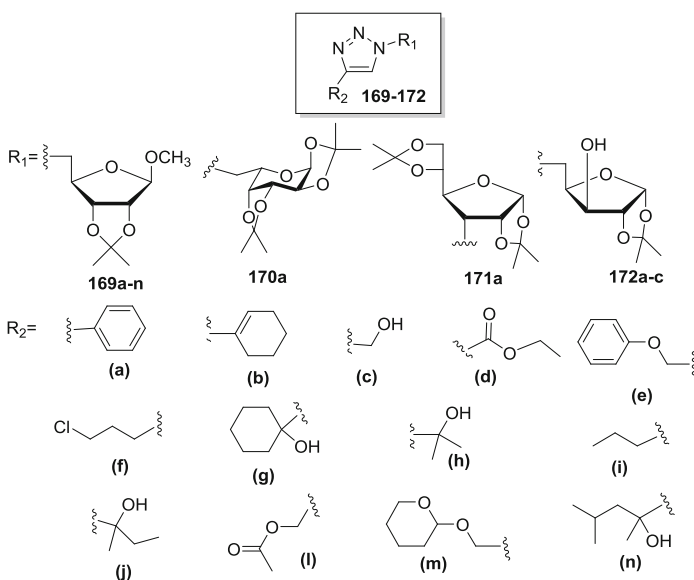


Fig. 15 Glycosyl 1H-1,2,3-triazoles (**169–172**) as antidiabetes candidates

indicates that this triazole series could represent new candidates for the development of novel drugs for the treatment of metabolic diseases, such as diabetes (Fig. 15).

Polyhydroxylated alkaloids have been isolated from plants and micro-organisms and are good glycosidase inhibitors that are potential therapeutic agents [260, 287]. For example, castanospermine (**173**), isolated from *Castanospermum*

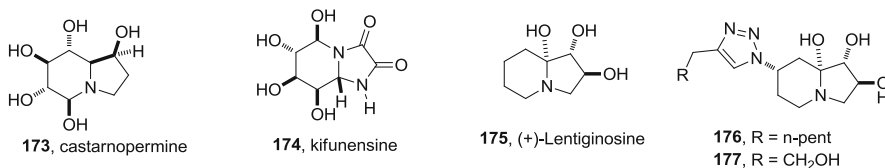


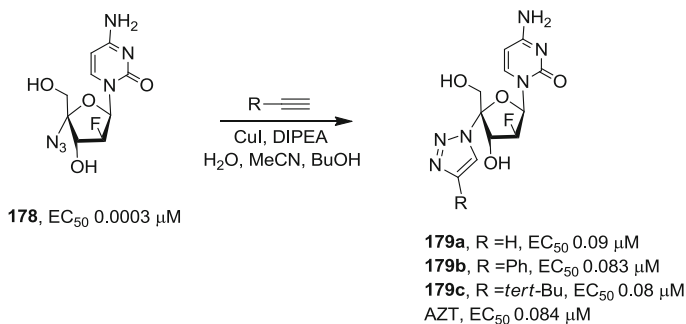
Fig. 16 Polyhydroxylated alkaloids from plants and triazole hybrids

australe, can inhibit both α -glucosidases and β -glucosidases [288], kifunensine (174), isolated from *Kitasatosporia kifunense*, showed its ability to act as an anticancer agent and α -mannosidase inhibitors [289], and (+)-lentiginosine (175), isolated from the leaves of *Astragalus lentiginosus*, among many others, is a good glycosidase inhibitor. Following the same pattern described above, new hybrid compounds of the piperidine or pyrrolidine alkaloids class tethered to triazole, tetrazole, pyrazole, or a pyrrole ring have been synthesized [263] and studied as inhibitors of various glycosidases. The triazoles 176 and 177 were synthesized based on the structure of (+)-lentiginosine (175) and showed better activities on β -glucosidase (EC 3.2.1.21) at 1 mM concentration than (+)-lentiginosine (175) (Fig. 16) [290].

The antiviral drug ribavirin (4, see Fig. 1) was used as inspiration for the synthesis of 2*H*-1,2,3-triazoles [291, 292], and compounds that mimic nucleosides [293] have been selected and synthesized [294] over the years to target enzymes of many infectious diseases. There are several drugs on the market for the treatment of diseases, such as human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV), based on this concept. Recently, Chang and coworkers reported the classical synthesis of several new 1,2,3-1*H*-triazole moieties at the 4'-C substituted-2'-deoxynucleosides, based on their past experience that most of the 4'-C substituted-2'-deoxynucleosides exhibited potent anti-HIV-1 activity without significant cytotoxicity [295, 296]. The evaluation of the triazole-nucleosides indicated that most of these compounds also exhibited potent anti-HIV-1 activity without significant cytotoxicity, and the best results (179a–c) are presented in Scheme 22 [297]. None of the compounds displayed better EC₅₀ values than the starting material (178) or AZT.

Recently, a novel class of deoxyribonucleosides having tropone-fused nitrogen heterocycles as nucleobases was prepared and presented weak antiviral activities for herpes simplex virus type 1 and herpes simplex virus type 2 compared with those of acyclovir (ACV). These nucleosides showed no cytotoxicity on a lung cancer cell line (A549) or on two colon (HT-29 and HCT-116) cancer cell lines.

Certain triazole compounds did not exhibit biological activity, and the linkage of this heterocycle with other moieties that have a recognized activity did not always increase the antimicrobial activity. This result occurred with the following compounds: 1,2,3-1*H*-triazole-tethered β -lactams (180) that were inactive against *M. tuberculosis* [298], 1,2,3-2*H*-triazole-tethered indole (181) as an antibacterial [299], hybrid compounds having 1,2,3-1*H*-triazole, piperidine, and



Scheme 22 Triazole-nucleosides as anti-HIV-1 prototypes

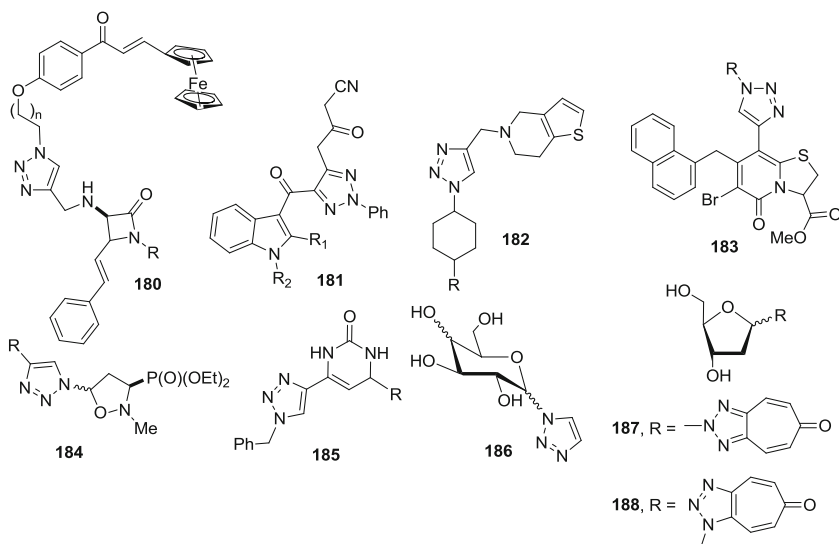


Fig. 17 Triazoles that exhibited no biological activity in their targets

tetrahydrothieno pyridine rings (**182**) showed the very modest antifungal activity (*Candida* spp.) [300], the series of triazole derivatives only exhibited very weak inhibition against α -glucosidase [301], triazoles that were ring-fused with 2-pyridones (**183**) showed low or no antibacterial activity [302], the *trans*- and *cis*-(1,2,3-triazolyl)isoxazolidinephosphonate series (**184**) were evaluated against a broad-spectrum of viruses but found not active at 250 μ M [303]; triazolyl dihydropyrimidine-2-thiones (**185**) were prepared by an efficient route, but most of them exhibited poor antibacterial activity compared with tetracycline [304], the glycosyl or galactosyl 1,2,3-triazoles (**186**) did not display inhibitory activity against the tested glycosidases [305], cyclohepta[d]triazol nucleosides (**187–188**) had weak antiviral activities against herpes simplex virus types 1 and 2 compared with acyclovir [306] (Fig. 17).

7 Conclusion

Drug discovery depends on the synthesis of a large group of small molecules that are easy to prepare and that can be active in biomolecule receptors and proteins. The triazole class fulfills these requirements, and they have been studied in recent years. This chapter demonstrated that this important class of heterocyclic compounds has attracted considerable attention because of their wide range of biological activities against various microorganisms, cells, and viruses and their inhibitory activities toward several enzymes. Due to the success of triazoles, some have entered the pharmaceutical market and are still being used as medicines. Many companies and research groups have shown interest in developing new methods for the synthesis and biological evaluation of these compounds. This class of compounds shows great potential as an antibacterial, antiprotozoal, anticancer, and inhibitor of the glucosidase enzymes, especially when incorporated into compounds containing other heterocyclic rings. There are two important aspects about these compounds. Hybrid triazole compounds with long chains that increase lipophilicity show enhanced permeation through the cell membranes and, thus, have enhanced inhibitory activity, and triazoles tethered to carbohydrates and other heterocycles have an increased number of hydrogen bonds and an increased number of interactions with bio-glycoconjugates on the surface of the microorganisms, thus, increasing their activities.

References

1. Yan ZY, Niu YN, Wei HL et al (2006) Combining proline and 'click chemistry': a class of versatile organocatalysts for the highly diastereo- and enantioselective Michael addition in water. *Tetrahedron Asymmetry* 17:3288–3293. doi:[10.1016/j.tetasy.2006.12.003](https://doi.org/10.1016/j.tetasy.2006.12.003)
2. Chandrasekhar S, Kumar TP, Haribabu K et al (2010) Hydroxyphthalimide allied triazole-pyrrolidine catalyst for asymmetric Michael additions in water. *Tetrahedron Asymmetry* 21:2372–2375. doi:[10.1016/j.tetasy.2010.08.012](https://doi.org/10.1016/j.tetasy.2010.08.012)
3. Chandrasekhar S, Kumar TP, Haribabu K et al (2010) Synthesis of hybrid 1,2,3-triazolo- δ -lactams/lactones using Huisgen [3+2] cycloaddition 'click-chemistry' in water. *Tetrahedron Asymmetry* 21:352–355. doi:[10.1016/j.tetasy.2010.02.002](https://doi.org/10.1016/j.tetasy.2010.02.002)
4. Zhao YB, Zhang LW, Wu LY et al (2008) Silica-supported pyrrolidine-triazole, an insoluble, recyclable organocatalyst for the enantioselective Michael addition of ketones to nitroalkenes. *Tetrahedron Asymmetry* 19:1352–1355. doi:[10.1016/j.tetasy.2008.05.011](https://doi.org/10.1016/j.tetasy.2008.05.011)
5. Zammit CM, Wills M (2013) Use of triazole-ring formation to attach a Ru/TsDPEN complex for asymmetric transfer hydrogenation to a soluble polymer. *Tetrahedron Asymmetry* 24:844–852. doi:[10.1016/j.tetasy.2013.05.022](https://doi.org/10.1016/j.tetasy.2013.05.022)
6. Yoshida Y, Takizawa S, Sasai H (2012) Design and synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids. *Tetrahedron Asymmetry* 23:843–851. doi:[10.1016/j.tetasy.2012.06.007](https://doi.org/10.1016/j.tetasy.2012.06.007)
7. Phillips OA, Udo EE, Abdel-Hamid ME et al (2009) Synthesis and antibacterial activity of novel 5-(4-methyl-1*H*-1,2,3-triazole) methyl oxazolidinones. *Eur J Med Chem* 44:3217–3227. doi:[10.1016/j.ejmech.2009.03.024](https://doi.org/10.1016/j.ejmech.2009.03.024)

8. Ferreira VF, da Rocha DR, da Silva FC et al (2013) Novel 1H-1,2,3-, 2H-1,2,3-, 1H-1,2,4- and 4H-1,2,4-triazole derivatives: a patent review (2008–2011). *Expert Opin Ther Pat* 23:319–331. doi:[10.1517.13543776.2013.749862](https://doi.org/10.1517/13543776.2013.749862)
9. Mandal SK, Saha D, Jain VK et al (2010) Synthesis and antitubercular activity of some triazole derivatives of propyl gallate. *Int J Pharm Sci Res* 1:465–472
10. Tan SL, Pause A, Shi V et al (2002) Hepatitis C Therapeutics: Current status and emerging Strategies. *Nature Rev Drug Discov* 1:867–881. doi:[10.1038/nrd937](https://doi.org/10.1038/nrd937)
11. Prusiner P, Sundaralingam M (1973) A new class of synthetic nucleoside analogues with broad-spectrum antiviral properties. *Nature New Biol* 244:116–118. doi:[10.1038/newbio244116a0](https://doi.org/10.1038/newbio244116a0)
12. Prusiner P, Sundaralingam M (1976) The crystal and molecular structures of two polymorphic crystalline forms of virazole (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). A new synthetic broad spectrum antiviral agent. *Acta Crystallogr B* 32:419–426. doi:[10.1107/S0567740876003154](https://doi.org/10.1107/S0567740876003154)
13. Smith RA, Knight V, Smith JAD (eds) (1984) Clinical applications of ribavirin. Academic, New York
14. Sidwell RW, Revankar GR, Robins RK (1985) Ribavirin: review of a broad-spectrum antiviral agent. In: Shugar D (ed) *Viral chemotherapy*. Pergamon, New York, pp 49–108
15. Melo JOF, Donnici CL, Augusti R et al (2006) Heterociclos 1,2,3 triazólicos: histórico, métodos de preparação, aplicações e atividades farmacológicas. *Quim Nova* 29:569–579. doi:[10.1590/S0100-40422006000300028](https://doi.org/10.1590/S0100-40422006000300028)
16. Aufort M, Herscovici J, Bouhours P et al (2008) Synthesis and antibiotic activity of a small molecules library of 1,2,3-triazole derivatives. *Bioorg Med Chem Lett* 18:1195–1198. doi:[10.1016/j.bmcl.2007.11.111](https://doi.org/10.1016/j.bmcl.2007.11.111)
17. Pereira D, Fernandes P (2011) Synthesis and antibacterial activity of novel 4-aryl-[1,2,3]-triazole containing macrolides. *Bioorg Med Chem Lett* 21:510–513. doi:[10.1016/j.bmcl.2010.10.091](https://doi.org/10.1016/j.bmcl.2010.10.091)
18. Lima-Neto RG, Cavalcante NNM, Srivastava RM et al (2012) Synthesis of 1,2,3-triazole derivatives and *in vitro* antifungal evaluation on *candida* strains. *Molecules* 17:5882–5892. doi:[10.3390/molecules17055882](https://doi.org/10.3390/molecules17055882)
19. Kategaonkar AH, Shinde PV, Kategaonkar AH et al (2010) Synthesis and biological evaluation of new 2-chloro-3-((4-phenyl-1H-1,2,3-triazol-1-yl)methyl)quinoline derivatives via click chemistry approach. *Eur J Med Chem* 45:3142–3146. doi:[10.1016/j.ejmech.2010.04.002](https://doi.org/10.1016/j.ejmech.2010.04.002)
20. Shalini K, Kumar N, Drabu S (2011) Advances in synthetic approach to and antifungal activity of triazoles. *Beilstein J Org Chem* 7:668–677. doi:[10.3762/bjoc.7.79](https://doi.org/10.3762/bjoc.7.79)
21. da Silva FC, de Souza MCBV, Frugulhetti ICPP et al (2009) Synthesis, HIV-RT inhibitory activity and SAR of 1-benzyl-1H-1,2,3-triazole derivatives of carbohydrates. *Eur J Med Chem* 44:373–383. doi:[10.1016/j.ejmech.2008.02.047](https://doi.org/10.1016/j.ejmech.2008.02.047)
22. Whiting M, Tripp JC, Lin Y-C et al (2006) Rapid discovery and structure-activity profiling of novel inhibitors of human immunodeficiency virus type 1 protease enabled by the copper(I)-catalyzed synthesis of 1,2,3-triazoles and their further functionalization. *J Med Chem* 49:7697–7710. doi:[10.1021/jm060754](https://doi.org/10.1021/jm060754)
23. Leaver DJ, Dawson RM, White JM et al (2011) Synthesis of 1,2,3-triazole linked galactopyranosides and evaluation of cholera toxin inhibition. *Org Biomol Chem* 9:8465–8474. doi:[10.1039/c1ob06317k](https://doi.org/10.1039/c1ob06317k)
24. Im C, Maiti SN, Micetich RG et al (1994) Synthesis and beta-lactamase inhibitory activity of 6-[(1-heteroarylthioethyl-1,2,3-triazol-4-yl)-methylene]penam sulfones. *J Antibiot* 47:1030–1040. doi:[10.7164/antibiotics.47.1030](https://doi.org/10.7164/antibiotics.47.1030)
25. Palhagen S, Canger R, Henriksen O et al (2001) Rufinamide: a double-blind, placebo-controlled proof of principle trial in patients with epilepsy. *Epilepsy Res* 43:115–124. doi:[10.1016/S0920-1211\(00\)00185-6](https://doi.org/10.1016/S0920-1211(00)00185-6)

26. Cunha AC, Figueiredo JM, Tributino JLM et al (2003) Antiplatelet properties of novel *N*-substituted-phenyl-1,2,3-triazole-4-acylhydrazones derivatives. *Bioorg Med Chem* 11:2051–2059. doi:[10.1016/S0968-0896\(03\)00055-5](https://doi.org/10.1016/S0968-0896(03)00055-5)
27. Jordão AK, Ferreira VF, Lima ES et al (2009) Synthesis, antiplatelet and in silico evaluations of novel *N*-substituted-phenylamino-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazides. *Bioorg Med Chem* 17:3713–3719. doi:[10.1016/j.bmc.2009.03.053](https://doi.org/10.1016/j.bmc.2009.03.053)
28. Menegatti R, Cunha AC, Ferreira VF et al (2003) Design, synthesis and pharmacological profile of novel dopamine D2 receptor ligands. *Bioorg Med Chem* 11:4807–4813. doi:[10.1016/S0968-0896\(03\)00487-5](https://doi.org/10.1016/S0968-0896(03)00487-5)
29. Biagi G, Dell'Omodarme G, Ferretti M et al (1990) Studies on 1,2,3-triazole derivatives as in vitro inhibitors of prostaglandin synthesis. *Farmaco* 45:1181–1192
30. Pelcman B, Sanin A, Nilsson P et al (2009) Triazole compounds as lipoxigenase inhibitors. US Patent 2009/0186918 A1, 23 July 2009
31. Assis SPO, Silva MT, Oliveira RN et al (2012) Synthesis and anti-inflammatory activity of new alkyl-substituted phthalimide 1*H*-1,2,3-triazole derivatives. *Scientific World J* 2012:1–7. doi:[10.1100/2012.9259.5](https://doi.org/10.1100/2012.9259.5)
32. Shafi S, Alam MM, Mulakayala N et al (2012) Synthesis of novel 2-mercapto benzothiazole and 1,2,3-triazole based bis-heterocycles: Their anti-inflammatory and anti-nociceptive activities. *Eur J Med Chem* 49:324–333. doi:[10.1016/j.ejmech.2012.01.032](https://doi.org/10.1016/j.ejmech.2012.01.032)
33. Biagi G, Dell'Omodarme G, Ferretti M et al (1992) Structure-activity studies on a 1,2,3-triazole derivative, a potent in vitro inhibitor of prostaglandin synthesis: the role of the heterocyclic ring. *Farmaco* 47:335–344
34. Biagi G, Ferretti M, Giorgi I et al (1993) 1,2,3-Triazole[4,5-*d*]pyridazines–I. Analogues of prostaglandin synthesis inhibitors. *Farmaco* 48:1159–1165
35. Buckle DR, Rockell CJ, Smith H et al (1984) Studies on 1,2,3-triazoles. 10. Synthesis and antiallergic properties of 9-oxo-1*H*,9*H*-benzothiopyrano[2,3-*d*]-1,2,3-triazoles and their *S*-oxides. *J Med Chem* 27:223–227. doi:[10.1021/jm00368a021](https://doi.org/10.1021/jm00368a021)
36. Buckle DR, Rockell CJ, Smith H et al (1986) Studies on 1,2,3-triazoles. 13. (Piperazinylalkoxy) [1]benzopyrano[2,3-*d*]-1,2,3-triazol-9(1*H*)-ones with combined H1-antihistamine and mast cell stabilizing properties. *J Med Chem* 29:2262–2267. doi:[10.1021/jm00161a022](https://doi.org/10.1021/jm00161a022)
37. Boechat N, Ferreira VF, Ferreira SB et al (2011) Novel 1,2,3-triazole derivatives for use against *Mycobacterium tuberculosis* H37Rv (ATCC 27294) strain. *J Med Chem* 54:5988–5999. doi:[10.1021/jm2003624](https://doi.org/10.1021/jm2003624)
38. Jordão AK, Sathler PC, Ferreira VF et al (2011) Synthesis, antitubercular activity, and SAR study of *N*-substituted-phenylamino-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazides. *Bioorg Med Chem* 19:5605–5611. doi:[10.1016/j.bmc.2011.07.035](https://doi.org/10.1016/j.bmc.2011.07.035)
39. Ferreira ML, de Souza MVN, Wardell SMSV et al (2010) Synthesis and antitubercular evaluation of new bis-1,2,3-triazoles derived from D-mannitol. *J Carbohydr Chem* 29:265–274. doi:[10.1080/07328303.2010.511749](https://doi.org/10.1080/07328303.2010.511749)
40. Wang X-L, Wan K, Zhou C-H (2010) Synthesis of novel sulfanilamide-derived 1,2,3-triazoles and their evaluation for antibacterial and antifungal activities. *Eur J Med Chem* 45:4631–4639. doi:[10.1016/j.ejmech.2010.07.031](https://doi.org/10.1016/j.ejmech.2010.07.031)
41. Reddy LVR, Reddy PV, Mishra NN et al (2010) Synthesis and biological evaluation of glycol-derived novel tetrahydrofuran 1,2,3-triazoles by 'click' chemistry. *Carbohydr Res* 345:1515–1521. doi:[10.1016/j.carres.2010.03.031](https://doi.org/10.1016/j.carres.2010.03.031)
42. Santos FC, Castro HC, Lourenço MC et al (2012) Tuberculosis: finding a new potential antimycobacterium derivative in a aldehyde-arylhydrazones-oxoquinoline series. *Curr Microbiol* 65:455–460. doi:[10.1007/s00284-012-0176-6](https://doi.org/10.1007/s00284-012-0176-6)
43. Jordão AK, Afonso PP, Ferreira VF et al (2009) Antiviral evaluation of *N*-amino-1,2,3-triazoles against Cantagalo virus replication in cell culture. *Eur J Med Chem* 44:3777–3783. doi:[10.1016/j.ejmech.2009.04.046](https://doi.org/10.1016/j.ejmech.2009.04.046)

44. Kelley JL, Koble CS, Davis RG et al (1995) 1-(Fluorobenzyl)-4-amino-1H-1,2,3-triazolo [4,5-c]pyridines: synthesis and anticonvulsant activity. *J Med Chem* 38:4131–4134. doi:[10.1021/jm00020a030](https://doi.org/10.1021/jm00020a030)
45. Junior ENS, de Moura MABF, Pinto AV et al (2009) Cytotoxic, trypanocidal activities and physicochemical parameters of nor- β -lapachone-based 1,2,3-triazoles. *J Braz Chem Soc* 20:635–643. doi:[10.1590/S0103-50532009000400007](https://doi.org/10.1590/S0103-50532009000400007)
46. Bakunov SA, Bakunova SM, Wenzler T et al (2010) Synthesis and antiprotozoal activity of cationic 1,4-diphenyl-1H-1,2,3-triazoles. *J Med Chem* 53:254–272. doi:[10.1021/jm901178d](https://doi.org/10.1021/jm901178d)
47. Ferreira SB, Costa MS, Boechat N (2007) Synthesis and evaluation of new difluoromethyl azoles as antileishmanial agents. *Eur J Med Chem* 42:1388–1395. doi:[10.1016/j.ejmech.2007.02.020](https://doi.org/10.1016/j.ejmech.2007.02.020)
48. Tahghighi A, Razmi S, Mahdavi M et al (2012) Synthesis and anti-leishmanial activity of 5-(5-nitrofuranyl)-1,3,4-thiadiazol-2-amines containing N-[(1-benzyl-1H-1,2,3-triazol-4-yl)methyl] moieties. *Eur J Med Chem* 50:124–128. doi:[10.1016/j.ejmech.2012.01.046](https://doi.org/10.1016/j.ejmech.2012.01.046)
49. Poulsen SA, Wilkinson BL, Innocenti A et al (2008) Inhibition of human mitochondrial carbonic anhydrases VA and VB with para-(4-phenyltriazole-1-yl)-benzenesulfonamide derivatives. *Bioorg Med Chem Lett* 18:4624–4627. doi:[10.1016/j.bmcl.2008.07.010](https://doi.org/10.1016/j.bmcl.2008.07.010)
50. Hou DR, Alam S, Kuan TC et al (2009) 1,2,3-Triazole derivatives as new cannabinoid CB1 receptor antagonists. *Bioorg Med Chem Lett* 19:1022–1025. doi:[10.1016/j.bmcl.2008.11.029](https://doi.org/10.1016/j.bmcl.2008.11.029)
51. Siles R, Kawasaki Y, Ross P et al (2011) Synthesis and biochemical evaluation of triazole/tetrazole-containing sulfonamides against thrombin and related serine proteases. *Bioorg Med Chem Lett* 21:5305–5309. doi:[10.1016/j.bmcl.2011.07.023](https://doi.org/10.1016/j.bmcl.2011.07.023)
52. Monceaux CJ, Hirata-Fukae C, Lam PC et al (2011) Triazole-linked reduced amide isosteres: an approach for the fragment-based drug discovery of anti-Alzheimer's BACE1 inhibitors. *Bioorg Med Chem Lett* 21:3992–3996. doi:[10.1016/j.bmcl.2011.05.007](https://doi.org/10.1016/j.bmcl.2011.05.007)
53. Wuest F, Tang X, Kniess T et al (2009) Synthesis and cyclooxygenase inhibition of various (aryl-1,2,3-triazole-1-yl)-methanesulfonylphenyl derivatives. *Bioorg Med Chem* 17:1146–1151. doi:[10.1016/j.bmc.2008.12.032](https://doi.org/10.1016/j.bmc.2008.12.032)
54. Yoon J, Cho L, Lee SK et al (2011) Syntheses of 1,2,3-triazolyl salicylamides with inhibitory activity on lipopolysaccharide-induced nitric oxide production. *Bioorg Med Chem Lett* 21:1953–1957. doi:[10.1016/j.bmcl.2011.02.034](https://doi.org/10.1016/j.bmcl.2011.02.034)
55. Jiang Y, Hansen TV (2011) Isatin 1,2,3-triazoles as potent inhibitors against caspase-3. *Bioorg Med Chem Lett* 21:1626–1629. doi:[10.1016/j.bmcl.2011.01.110](https://doi.org/10.1016/j.bmcl.2011.01.110)
56. Bahadoor A, Castro AC, Chan LK et al (2011) Triazoles as inhibitors of fatty acid synthase. US Patent 2011/0274654 A1, 10 Nov 2011
57. Lo Conte M, Marra A, Chambery A et al (2010) Modular approach to triazole-linked 1,6- α -D-oligomannosides to the discovery of inhibitors of *Mycobacterium tuberculosis* cell wall synthetase. *J Org Chem* 75:6326–6336. doi:[10.1021/jo100928g](https://doi.org/10.1021/jo100928g)
58. Hinou H, Miyoshi R, Takasu Y et al (2011) A strategy for neuraminidase inhibitors using mechanism-based labeling information. *Chem Asian J* 6:1048–1056. doi:[10.1002/asia.201000594](https://doi.org/10.1002/asia.201000594)
59. Kai H, Hinou H, Nishimura SI (2012) Aglycone-focused randomization of 2-difluoromethylphenyl-type sialoside suicide substrates for neuraminidases. *Bioorg Med Chem* 20:2739–2746. doi:[10.1016/j.bmc.2012.02.001](https://doi.org/10.1016/j.bmc.2012.02.001)
60. Campos VR, Abreu PA, Castro HC et al (2009) Synthesis, biological, and theoretical evaluations of new 1,2,3-triazoles against the hemolytic profile of the *Lachesis muta* snake venom. *Bioorg Med Chem* 17:7429–7434. doi:[10.1016/j.bmc.2009.09.031](https://doi.org/10.1016/j.bmc.2009.09.031)
61. Tong W, Wu JC, Sandstrom A et al (1990) Synthesis of new 2',3'-dideoxy-2',3'- α -fused-heterocyclic uridines, & some 2', 3'-ene-2'-substituted uridines from easily accessible 2',3'-ene-3'-phenylselenonyl uridine. *Tetrahedron* 46:3037–3060. doi:[10.1016/S0040-4020\(01\)88395-2](https://doi.org/10.1016/S0040-4020(01)88395-2)

62. Domingos TFS, Moura LA, Carvalho C et al (2013) Antivenom effects of 1,2,3-triazoles against *Bothrops jararaca* and *Lachesis muta* snakes. *BioMed Res Int* 2013:1–7. doi:[10.1155.2013.2942.9](https://doi.org/10.1155/2013.2942.9)
63. Borgati TF, Alves RB, Teixeira RR et al (2013) Synthesis and phytotoxic activity of 1,2,3-triazole derivatives. *J Braz Chem Soc* 24:953–961. doi:[10.5935.0103.5053.20130121](https://doi.org/10.5935/0103.5053.20130121)
64. Raj R, Singh P, Singh P et al (2013) Azide-alkyne cycloaddition en route to 1*H*-1,2,3-triazole-tethered 7-chloroquinoline-isatin chimeras: Synthesis and antimalarial Evaluation. *Eur J Med Chem* 62:590–596. doi:[10.1016/j.ejmech.2013.01.032](https://doi.org/10.1016/j.ejmech.2013.01.032)
65. Therin C, Levesque RC (2000) Molecular basis of antibiotic resistance and β -lactamase inhibition by mechanism-based inactivators: Perspectives and future directions. *FEMS Microbiol Rev* 24:251–262
66. Khan FY, Elhiday A, Khudair IF et al (2012) Evaluation of the use of piperacillin/tazobactam (Tazocin®) at Hamad General Hospital, Qatar: Are there unjustified prescriptions? *Infect Drug Resist* 5:17–21. doi:[10.2147/IDR.S27965](https://doi.org/10.2147/IDR.S27965)
67. Blackwell CC, Freimer EH, Tuke GC (1976) *In vitro* evaluation of the new oral cephalosporin cefatrizine: comparison with other cephalosporins. *Antimicrob Agents Chemother* 10:288–292. doi:[10.1128/AAC.10.2.288](https://doi.org/10.1128/AAC.10.2.288)
68. Corrado C, Flugy AM, Taverna S et al (2012) Carboxyamidotriazole-orotate inhibits the growth of imatinib-resistant chronic myeloid leukaemia cells and modulates exosomes-stimulated angiogenesis. *PLoS One* 7:e42310. doi:[10.1371/journal.pone.0042310](https://doi.org/10.1371/journal.pone.0042310)
69. Agalave SG, Maujan SR, Pore VS (2011) Click chemistry: 1,2,3-Triazoles as pharmacophores. *Chem Asian J* 6:2696–2718. doi:[10.1002/asia.201100432](https://doi.org/10.1002/asia.201100432)
70. Das K, Bauman JD, Rim AS et al (2011) Crystal structure of tert-butyldimethylsilyl-spiroamino oxathioledioxide-thymine (TSAO-T) in complex with HIV-1 reverse transcriptase (RT) redefines the elastic limits of the non-nucleoside inhibitor-binding pocket. *J Med Chem* 54:2727–2737. doi:[10.1021/jm101536x](https://doi.org/10.1021/jm101536x)
71. Pérez-Castro I, Caamaño O, Fernández F et al (2007) Synthesis of 4-substituted-1,2,3-triazole carbanucleoside analogues of ribavirin via click chemistry. *Org Biomol Chem* 5:3805–3813. doi:[10.1039/B710348D](https://doi.org/10.1039/B710348D)
72. Lahann J (ed) (2009) Click chemistry for biotechnology and materials science. Wiley, Michigan. doi:[10.1002.978047074.8.2](https://doi.org/10.1002.978047074.8.2)
73. Wang T, Hu XC, Huang XJ et al (2012) Efficient synthesis of functionalized 1,2,3-Triazoles by catalyst-free 1,3-dipolar cycloaddition of nitroalkenes with sodium azide. *J Braz Chem Soc* 23:1119–1123. doi:[10.1590/S0103-50532012000600017](https://doi.org/10.1590/S0103-50532012000600017)
74. Fiandanese V, Maurantonio S, Punzi A et al (2012) A general procedure for the synthesis of alkyl- and arylolethynyl-1,2,3-triazole-fused dihydroisoquinolines. *Org Biomol Chem* 10:1186–1195. doi:[10.1039/c1ob06701j](https://doi.org/10.1039/c1ob06701j)
75. Benhaoua C (2012) New 1,2,3 triazole iminosugars derivatives using click chemistry. *Int J Carbohydr Chem* 2012:1–10. doi:[10.1155/2012.3945.4](https://doi.org/10.1155/2012.3945.4)
76. Yap AH, Weinreb SM (2006) β -Tosylethylazide: a useful synthon for preparation of N-protected 1,2,3-triazoles via click chemistry. *Tetrahedron Lett* 47:3035–3038. doi:[10.1016/j.tetlet.2006.03.020](https://doi.org/10.1016/j.tetlet.2006.03.020)
77. Silva BNM, Silva BV, da Silva FC et al (2013) Synthesis of novel isatin-type 5'-(4-alkyl/aryl-1*H*-1,2,3-triazoles) via 1,3-dipolar cycloaddition reactions. *J Braz Chem Soc* 24:179–183. doi:[10.5935.0103.5053.20130023](https://doi.org/10.5935/0103.5053.20130023)
78. da Silva MT, de Oliveira RN, Valença WO et al (2012) Synthesis of *N*-substituted phthalimidoalkyl 1*H*-1,2,3-triazoles: a molecular diversity combining click chemistry and ultrasound irradiation. *J Braz Chem Soc* 23:1839–1843. doi:[10.1590/S0103-50532012005000053](https://doi.org/10.1590/S0103-50532012005000053)
79. Barbosa FCG, de Oliveira RN (2011) Synthesis of a new class of triazole-linked benzoheterocycles via 1,3-dipolar cycloaddition. *J Braz Chem Soc* 22:592–597. doi:[10.1590/S0103-50532011000300025](https://doi.org/10.1590/S0103-50532011000300025)

80. Huisgen R (1963) 1,3-Dipolare cycloadditionen rückschau und ausblick. *Angew Chem* 75:604–637. doi:[10.1002/ange.19630751304](https://doi.org/10.1002/ange.19630751304)
81. Huisgen R (1963) Kinetik und mechanismus 1,3-dipolarer cycloadditionen. *Angew Chem* 75:742–754. doi:[10.1002/ange.19630751603](https://doi.org/10.1002/ange.19630751603)
82. Huisgen R (1963) Kinetics and mechanism of 1,3-dipolar cycloadditions. *Angew Chem Int Ed Engl* 2:633–645. doi:[10.1002/anie.196306331](https://doi.org/10.1002/anie.196306331)
83. Kolb HC, Sharpless KB (2003) The growing impact of click chemistry on drug discovery. *Drug Discov Today* 8:1128–1137. doi:[10.1016/S1359-6446\(03\)02933-7](https://doi.org/10.1016/S1359-6446(03)02933-7)
84. Wu P, Fokin VV (2007) Catalytic azide-alkyne cycloaddition: reactivity and applications. *Aldrichim Acta* 40:7–17
85. Zhang L, Chen X, Xue P et al (2005) Ruthenium-catalyzed cycloaddition of alkynes and organic azides. *J Am Chem Soc* 127:15998–15999. doi:[10.1021/ja054114s](https://doi.org/10.1021/ja054114s)
86. Dondoni A (2007) Triazole: the keystone in glycosylated molecular architectures constructed by a click reaction. *Chem Asian J* 2:700–708. doi:[10.1002/asia.200700015](https://doi.org/10.1002/asia.200700015)
87. Freitas LBO, Ruela FA, Pereira GR et al (2011) A Reação “Click” na Síntese De 1,2,3-Triazóis: Aspectos Químicos e Aplicações. *Quim Nova* 34:1791–1804. doi:[10.1590/S0100-40422011001000012](https://doi.org/10.1590/S0100-40422011001000012)
88. Zarei RA, Khazdooz L, Hajipour AR et al (2012) Microwave-assisted click chemistry synthesis of 1,2,3-triazoles from aryldiazonium silica sulfates in water. *Synthesis* 3353–3360. doi:[10.1055/s-0032-1316783](https://doi.org/10.1055/s-0032-1316783)
89. Jlalía I, Meganem F, Herscovici J et al (2009) “Flash” solvent-free synthesis of triazoles using a supported catalyst. *Molecules* 14:528–539. doi:[10.3390/molecules14010528](https://doi.org/10.3390/molecules14010528)
90. Martinelli M, Milcent T, Ongeri S et al (2008) Synthesis of new triazole-based trifluoromethyl scaffolds. *Beilstein J Org Chem* 4:1–4. doi:[10.3762/bjoc.4.19](https://doi.org/10.3762/bjoc.4.19)
91. Bock VD, Hiemstra H, Van Maarseveen JH (2006) CuI-catalyzed alkyne–azide “click” cycloadditions from a mechanistic and synthetic perspective. *Eur J Org Chem* 2006:51–68. doi:[10.1002/ejoc.200500483](https://doi.org/10.1002/ejoc.200500483)
92. MacDonald JP, Badillo JJ, Arevalo GE et al (2012) Catalytic stereoselective synthesis of diverse oxindoles and spirooxindoles from isatins. *ACS Comb Sci* 14:285–293. doi:[10.1021/co300003c](https://doi.org/10.1021/co300003c)
93. Aragão-Leoneti V, Campo VL, Gomes AS et al (2010) Application of copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) ‘click chemistry’ in carbohydrate drug and neoglycopolymers synthesis. *Tetrahedron* 66:9475–9492. doi:[10.1016/j.tet.2010.10.001](https://doi.org/10.1016/j.tet.2010.10.001)
94. Junior ENS, Guimarães TT, Menna-Barreto RF et al (2010) The evaluation of quinonoid compounds against *Trypanosoma cruzi*: synthesis of imidazolic anthraquinones, nor-beta-lapachone derivatives and beta-lapachone-based 1,2,3-triazoles. *Bioorg Med Chem* 18:3224–3230. doi:[10.1016/j.bmc.2010.03.029](https://doi.org/10.1016/j.bmc.2010.03.029)
95. Zhang F, Moses JE (2009) Benzyne click chemistry with in situ generated aromatic azides. *Org Lett* 11:1587–1590. doi:[10.1021/ol9002338](https://doi.org/10.1021/ol9002338)
96. Beckmann HS, Möller HM, Wittmann V (2012) High-affinity multivalent wheat germ agglutinin ligands by one-pot click reaction. *Beilstein J Org Chem* 8:819–826. doi:[10.3762/bjoc.8.91](https://doi.org/10.3762/bjoc.8.91)
97. Zhang J, Jin G, Xiao S (2013) Novel synthesis of 1,4,5-trisubstituted 1,2,3-triazoles via a one-pot three-component reaction of boronic acids, azide, and active methylene ketones. *Tetrahedron* 69:2352–2356. doi:[10.1016/j.tet.2012.12.086](https://doi.org/10.1016/j.tet.2012.12.086)
98. Angell YL, Burgess K (2007) Peptidomimetics via copper-catalyzed azide-alkyne cycloadditions. *Chem Soc Rev* 36:1674–1689. doi:[10.1039/B701444A](https://doi.org/10.1039/B701444A)
99. Pedersen DS, Abell A (2011) 1,2,3-Triazoles in peptidomimetic chemistry. *Eur J Org Chem* 2011:2399–2411. doi:[10.1002/ejoc.201100157](https://doi.org/10.1002/ejoc.201100157)
100. Chrysina ED, Bokor E, Alexacou KM (2009) Amide-1,2,3-triazole bioisosterism: the glycogen phosphorylase case. *Tetrahedron Asymmetry* 20:733–740. doi:[10.1016/j.tetasy.2009.03.021](https://doi.org/10.1016/j.tetasy.2009.03.021)

101. Bock VD, Speijer D, Hiemstra H et al (2007) 1,2,3-Triazoles as peptide bond isosteres: synthesis and biological evaluation of cyclotetrapeptide mimics. *Org Biomol Chem* 5:971–975. doi:[10.1039/b616751a](https://doi.org/10.1039/b616751a)
102. Horne WS, Yadav MK, Stout CD et al (2004) Heterocyclic peptide backbone modifications in an alpha-helical coiled coil. *J Am Chem Soc* 126:15366–15367. doi:[10.1021/ja0450408](https://doi.org/10.1021/ja0450408)
103. Bezouska K (2002) Design, functional evaluation and biomedical applications of carbohydrate dendrimers (glycodendrimers). *Rev Mol Biotechnol* 90:269–290. doi:[10.1016/S1389-0352\(01\)00064-2](https://doi.org/10.1016/S1389-0352(01)00064-2)
104. Vatmurge NS, Hazra BG, Pore VS et al (2008) Synthesis and antimicrobial activity of beta-lactam-bile acid conjugates linked via triazole. *Bioorg Med Chem Lett* 18:2043. doi:[10.1016/j.bmcl.2008.01.102](https://doi.org/10.1016/j.bmcl.2008.01.102)
105. Whiting M, Muldoon J, Lin YC et al (2006) Inhibitors of HIV-1 protease by using in situ click chemistry. *Angew Chem Int Ed* 45:1435–1439. doi:[10.1002/anie.200502161](https://doi.org/10.1002/anie.200502161)
106. Sharma P, Kumar A, Upadhyay S et al (2010) A novel approach to the synthesis of 1,2,3 triazoles and their SAR studies. *Med Chem Res* 19:589–602. doi:[10.1007/s00044-009-9215-7](https://doi.org/10.1007/s00044-009-9215-7)
107. Košmrlj J (ed) (2012) Click triazoles. Springer, Berlin Heidelberg
108. Kamijo S, Jin T, Huo Z et al (2002) Regiospecific synthesis of 2-allyl-1,2,3-triazoles by palladium-catalyzed 1,3-dipolar cycloaddition. *Tetrahedron Lett* 43:9707–9710. doi:[10.1016/S0040-4039\(02\)02206-2](https://doi.org/10.1016/S0040-4039(02)02206-2)
109. Liu Y, Yan W, Chen Y et al (2008) Efficient synthesis of N-2-Aryl-1,2,3-Triazole fluorophores via post-triazole arylation. *Org Lett* 10:5389–5392. doi:[10.1021/ol802246q](https://doi.org/10.1021/ol802246q)
110. Ghoslan SAS, Abdelhamid IAA, Ibrahim HM et al (2006) Studies with 2-arylhydrazonitriles: a new convenient synthesis of 2,4-disubstituted-1,2,3-triazole-5-amines. *Arkivoc* XV:53–60
111. Kalisiak J, Sharpless KB, Fokin VV (2008) Efficient synthesis of 2-substituted-1,2,3-triazoles. *Org Lett* 10:3171–3174. doi:[10.1021/ol8006748](https://doi.org/10.1021/ol8006748)
112. Jiang Y, Kuang C (2013) Recent advances in the synthesis of 1-monosubstituted 1,2,3-triazoles. *Mini Rev Med Chem* 13:713–719. doi:[10.2174.138955751131305.0.8](https://doi.org/10.2174/138955751131305.0.8)
113. Koszytkowska-Stawinska M, Mironiuk-Puchalska E, Rowicki T (2012) Synthesis of 1,2,3-triazolo-nucleosides via the post-triazole N-alkylation. *Tetrahedron* 68:214–225. doi:[10.1016/j.tet.2011.10.067](https://doi.org/10.1016/j.tet.2011.10.067)
114. Caliendo G, Fiorino F, Grieco P et al (1999) Preparation and local anaesthetic activity of benzotriazinone and benzoyltriazole derivatives. *Eur J Med Chem* 3:1043–1051. doi:[10.1016/S0223-5234\(99\)00126-9](https://doi.org/10.1016/S0223-5234(99)00126-9)
115. Blass BB, Coburn K, Lee W et al (2006) Synthesis and evaluation of (2-phenethyl-2*H*-1,2,3-triazol-4-yl)(phenyl)methanones as Kv1.5 channel blockers for the treatment of atrial fibrillation. *Bioorg Med Chem Lett* 16:4629–4632. doi:[10.1016/j.bmcl.2006.06.001](https://doi.org/10.1016/j.bmcl.2006.06.001)
116. Sanna P, Carta A, Nikoobar MER (2000) Synthesis and antitubercular activity of 3-aryl substituted-2-(1*H*(2*H*) benzotriazol-1(2)-yl)acrylonitriles. *Eur J Med Chem* 35:535–543. doi:[10.1016/S0223-5234\(00\)00144-6](https://doi.org/10.1016/S0223-5234(00)00144-6)
117. von Mutius E, Drazen JM (2012) 200th anniversary article: a patient with asthma seeks medical advice in 1828, 1928, and 2012. *N Engl J Med* 366:827–834. doi:[10.1056/NEJMr1102783](https://doi.org/10.1056/NEJMr1102783)
118. Coe MD, Cooper JWA, Gore MP et al (2010) Preparation of pyrazole and triazole carboxamides as CRAC channel inhibitors. WO2010122088, 2010
119. Keivanloo A, Bakherad M, Taheri SAN (2013) One-pot synthesis of 4,5-disubstituted 1,2,3-(*NH*)-triazoles by silica supported-zinc bromide in the aerobic condition. *C R Chimie* 16:239–243. doi:[10.1016/j.crci.2012.11.007](https://doi.org/10.1016/j.crci.2012.11.007)
120. Ueda S, Su M, Buchwald SL (2011) Highly N2-selective palladium-catalyzes arylation of 1,2,3 triazoles. *Angew Chem Int Ed* 50:8944–8947. doi:[10.1002/anie.201103882](https://doi.org/10.1002/anie.201103882)
121. Abdel-Wahab BF, Abdel-Latif E, Mohamed HA et al (2012) Design and synthesis of new 4-pyrazolin-3-yl-1,2,3-triazoles and 1,2,3-triazol-4-yl-pyrazolin-1-ylthiazoles as potential antimicrobial agents. *Eur J Med Chem* 52:263–268. doi:[10.1016/j.ejmech.2012.03.023](https://doi.org/10.1016/j.ejmech.2012.03.023)

122. World Health Organization (2012) Health topics. Tuberculosis. <http://www.who.int/topics/tuberculosis/en/>. Accessed 13 Dec 2012
123. World Health Organization (2012) Global Health Observatory (GHO). Tuberculosis (TB). <http://www.who.int/gho/tb/en/>. Accessed 13 Dec 2012
124. World Health Organization (2012) Media centre. Tuberculosis, Fact sheet No. 104. <http://www.who.int/mediacentre/factsheets/fs104/en/index.html>. Accessed 13 Dec 2012
125. Nogueira AF, Facchinetti V, de Souza MVN et al (2012) Tuberculose: uma abordagem geral dos principais aspectos. *Rev Bras Farm* 93:3–9
126. World Health Organization (2012) Global tuberculosis report 2012. http://www.who.int/tb/publications/global_report/en/. Accessed 7 Jan 2013
127. Brunton LL, Chabmer AA, Knollman BC (2011) Goodman & Gilman's the pharmacological basis of therapeutics, 12th edn. McGraw-Hill, New York
128. Katzung BG (2010) Farmacologia básica e clínica, 10th edn. AMGH, Porto Alegre
129. Janin Y (2007) Antituberculosis drugs: ten years of research. *Bioorg Med Chem* 15:2479–2513. doi:[10.1016/j.bmc.2007.01.030](https://doi.org/10.1016/j.bmc.2007.01.030)
130. Branco FSC, Pinto AC, Boechat N (2012) A química medicinal de novas moléculas em fase clínica para o tratamento da tuberculose. *Rev Virtual Quim* 4:287–328
131. Andries K, Verhasselt P, Guillemont J et al (2005) Diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science* 307:223–227. doi:[10.1126/science.1106753](https://doi.org/10.1126/science.1106753)
132. Barbachyn MR, Hutchinson DK, Brickner SJ (1996) Identification of a novel oxazolidinone (U-100480) with potent antimycobacterial activity. *J Med Chem* 39:680–685. doi:[10.1021/jm950956y](https://doi.org/10.1021/jm950956y)
133. Sasaki H, Haraguchi Y, Itotani M et al (2006) Synthesis and antituberculosis activity of a novel series of optically active 6-Nitro-2,3-dihydroimidazo[2,1-b]oxazoles. *J Med Chem* 49:7854–7860. doi:[10.1021/jm060957y](https://doi.org/10.1021/jm060957y)
134. Stover CK, Warrenner P, Van Devanter DR et al (2000) A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. *Nature* 405:962–966. doi:[10.1038.3501.1.3](https://doi.org/10.1038.3501.1.3)
135. Umesiri FE, Sanki AK, Boucau J et al (2010) Recent advances toward the inhibition of mAG and LAM synthesis in *Mycobacterium tuberculosis*. *Med Res Rev* 30:290–326. doi:[10.1002/med.20190](https://doi.org/10.1002/med.20190)
136. Tizon L, Otero JM, Prazeres VFV et al (2011) A Prodrug approach for improving antituberculosis activity of potent *Mycobacterium tuberculosis* type II dehydroquinase inhibitors. *J Med Chem* 54:6063–6084. doi:[10.1021/jm2006063](https://doi.org/10.1021/jm2006063)
137. Gadhave PP, Dighe NS, Pattan SR et al (2010) Current biological and synthetic profile of triazoles: a review. *Annals Biol Res* 1:82–89
138. Kharb R, Sharma PC, Yar MS (2011) Pharmacological significance of triazole scaffold. *J Enzyme Inhib Med Chem* 26:1–21. doi:[10.3109.1475636090352.3.4](https://doi.org/10.3109.1475636090352.3.4)
139. Kharb R, Yar MS, Sharma PC (2011) Recent advances and future perspectives of triazole analogs as promising antiviral. *Mini Rev Med Chem* 11:84–96. doi:[10.2174.13895571179356.0.1](https://doi.org/10.2174.13895571179356.0.1)
140. Stefely JA, Palchaudhuri R, Miller PA et al (2010) N-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)arylamide as a new scaffold that provides rapid access to antimicrotubule agents: synthesis and evaluation of antiproliferative activity against select cancer cell lines. *J Med Chem* 53:3389–3395. doi:[10.1021/jm1000979](https://doi.org/10.1021/jm1000979)
141. Campo VL, Sesti-Costa R, Carneiro ZA et al (2012) Design, synthesis and the effect of 1,2,3-triazole sialylmimetic neoglycoconjugates on *Trypanosoma cruzi* and its cell surface trans-sialidase. *Bioorg Med Chem* 20:145–156. doi:[10.1016/j.bmc.2011.11.022](https://doi.org/10.1016/j.bmc.2011.11.022)
142. Gallardo H, Conte G, Bryk F et al (2007) Synthesis and evaluation of 1-Alkyl-4-phenyl-[1,2,3]triazole derivatives as antimycobacterial agent. *J Braz Chem* 18:1285–1291. doi:[10.1590/S0103-50532007000600027](https://doi.org/10.1590/S0103-50532007000600027)

143. Maccari R, Ottana R, Vigorita MG (2005) In vitro advanced antimycobacterial screening of isoniazid-related hydrazones, hydrazides and cyanoboranes: part 14. *Bioorg Med Chem Lett* 15:2509–2513. doi:[10.1016/j.bmcl.2005.03.065](https://doi.org/10.1016/j.bmcl.2005.03.065)
144. Lima CH, Henriques MG, Candéa AL et al (2011) Synthesis and antimycobacterial evaluation of N-(E)-heteroaromaticpyrazine-2-carbohydrazide derivatives. *Med Chem* 7:245–249. doi:[15.3.40.4.11](https://doi.org/10.1533/04.11)
145. Ferreira ML, Gonçalves RS, Cardoso LN et al (2010) Synthesis and antitubercular activity of heteroaromatic isonicotinoyl and 7-chloro-4-quinolinyl hydrazone derivatives. *Scientific-WorldJournal* 10:1347–1355. doi:[10.1100/tsw.2010.124](https://doi.org/10.1100/tsw.2010.124)
146. Vilcheze C, Morbidoni HR, Weisbrod TR et al (2000) Inactivation of the inhA-encoded fatty acid synthase II (FASII) enoyl-acyl carrier protein reductase induces accumulation of the FASI end products and cell lysis of *Mycobacterium smegmatis*. *J Bacteriol* 182:4059–4067. doi:[10.1128/JB.182.14.4059-4067.2000](https://doi.org/10.1128/JB.182.14.4059-4067.2000)
147. Freundlich JS, Wang F, Vilchèze C et al (2009) Triclosan derivatives: towards potent inhibitors of drug-sensitive and drug-resistant *Mycobacterium tuberculosis*. *ChemMedChem* 4:241–248. doi:[10.1002/cmdc.200800261](https://doi.org/10.1002/cmdc.200800261)
148. Menendez C, Chollet A, Rodriguez F et al (2012) Chemical synthesis and biological evaluation of triazole derivatives as inhibitors of InhA and antituberculosis agents. *Eur J Med Chem* 52:275–283. doi:[10.1016/j.ejmech.2012.03.029](https://doi.org/10.1016/j.ejmech.2012.03.029)
149. Labadie GR, de la Iglesia A, Morbidoni HR (2011) Targeting tuberculosis through a small focused library of 1,2,3-triazoles. *Mol Divers* 15:1017–1024. doi:[10.1007/s11030-011-9319-0](https://doi.org/10.1007/s11030-011-9319-0)
150. Menendez C, Gaua S, Lherbeta C et al (2011) Synthesis and biological activities of triazole derivatives as inhibitors of InhA and antituberculosis agents. *J Eur Chem* 46:5524–5531. doi:[10.1016/j.ejmech.2011.09.013](https://doi.org/10.1016/j.ejmech.2011.09.013)
151. Ouellet H, Podust LM, de Montellano PR (2008) *Mycobacterium tuberculosis* CYP130: crystal structure, biophysical characterization, and interactions with antifungal azole drugs. *J Biol Chem* 283(28):5069–5080. doi:[10.1074/jbc.M708734200](https://doi.org/10.1074/jbc.M708734200)
152. Kim PH, Kim SH, Lee SH et al (2011) Preparation of triazole compounds for treatment of tuberculosis. *KR* 2011046186 A
153. Shanmugavelan P, Nagarajan S, Sathishkumar M et al (2011) Efficient synthesis and in vitro antitubercular activity of 1,2,3-triazoles as inhibitors of *Mycobacterium tuberculosis*. *Bioorg Med Chem Lett* 21:7273–7276. doi:[10.1016/j.bmcl.2011.10.048](https://doi.org/10.1016/j.bmcl.2011.10.048)
154. Crick DC, Mahapatra S, Brennan PJ (2001) Biosynthesis of the arabinogalactan-peptidoglycan complex of *Mycobacterium tuberculosis*. *Glycobiology* 11:107–118. doi:[10.1093/glycob/11.9.107R](https://doi.org/10.1093/glycob/11.9.107R)
155. Cao B, White JM, Williams SJ (2011) Synthesis of glycoconjugate fragments of mycobacterial phosphatidylinositol mannosides and lipomannan. *Beilstein J Org Chem* 7:369–377. doi:[10.3762/bjoc.7.47](https://doi.org/10.3762/bjoc.7.47)
156. Wilkinson BL, Long H, Sim E et al (2008) Synthesis of Arabino glycosyl triazoles as potential inhibitors of mycobacterial cell wall biosynthesis. *Bioorg Med Chem Lett* 18:6265–6267. doi:[10.1016/j.bmcl.2008.09.082](https://doi.org/10.1016/j.bmcl.2008.09.082)
157. Singh BK, Yadav AK, Kumar B et al (2008) Preparation and reactions of sugar azides with alkynes: synthesis of sugar triazoles as antitubercular agents. *Carbohydr Res* 343:1153–1162. doi:[10.1016/j.carres.2008.02.013](https://doi.org/10.1016/j.carres.2008.02.013)
158. Gupte A, Boshoff HI, Wilson DJ et al (2008) Inhibition of siderophore biosynthesis by 2-triazole substituted analogues of 5'-O-[N-(salicyl)sulfamoyl]adenosine: antibacterial nucleosides effective against *Mycobacterium tuberculosis*. *J Med Chem* 51:7495–7507. doi:[10.1021/jm8008037](https://doi.org/10.1021/jm8008037)
159. Chen L, Gao G, Bonnac L et al (2007) Methylenebis(sulfonamide) linked nicotinamide adenine dinucleotide analogue as an inosine monophosphate dehydrogenase inhibitor. *Bioorg Med Chem Lett* 17:3152–3155. doi:[10.1016/j.bmcl.2007.03.035](https://doi.org/10.1016/j.bmcl.2007.03.035)

160. Lesiak K, Watanabe KA, Majumdar A et al (1998) Synthesis of a methylenebis(phosphonate) analogue of mycophenolic adenine dinucleotide: a glucuronidation-resistant MAD analogue of NAD. *J Med Chem* 41:618–622. doi:[10.1021/jm970705k](https://doi.org/10.1021/jm970705k)
161. Pankiewicz KW, Lesiak-Watanabe KB, Watanabe KA et al (2002) Novel mycophenolic adenine bis(phosphonate) analogues as potential differentiation agents against human leukemia. *J Med Chem* 45:703–712. doi:[10.1021/jm0104116](https://doi.org/10.1021/jm0104116)
162. Chen L, Wilson DJ, Xu Y et al (2010) Triazole-linked inhibitors of inosine monophosphate dehydrogenase from human and *Mycobacterium tuberculosis*. *J Med Chem* 53:4768–4778. doi:[10.1021/jm100424m](https://doi.org/10.1021/jm100424m)
163. Gill C, Jadhav G, Shaikh M et al (2008) Clubbed [1,2,3] triazoles by fluorine benzimidazole: A novel approach to H37Rv inhibitors as a potential treatment for tuberculosis. *Bioorg Med Chem Lett* 18:6244–6247. doi:[10.1016/j.bmcl.2008.09.096](https://doi.org/10.1016/j.bmcl.2008.09.096)
164. Castagnolo D, Radi M, Dessì F et al (2009) Synthesis and biological evaluation of new enantiomerically pure azole derivatives as inhibitors of *Mycobacterium tuberculosis*. *Bioorg Med Chem Lett* 19:2203–2205. doi:[10.1016/j.bmcl.2009.02.101](https://doi.org/10.1016/j.bmcl.2009.02.101)
165. Tripathi RP, Yadav AK, Ajay A et al (2010) Application of Huisgen (3+2) cycloaddition reaction: Synthesis of 1-(2,3-dihydrobenzofuran-2-yl)-methyl [1,2,3]-triazoles and their antitubercular evaluations. *Eur J Med Chem* 45:142–148. doi:[10.1016/j.ejmech.2009.09.036](https://doi.org/10.1016/j.ejmech.2009.09.036)
166. Patpi SR, Pulipati L, Yogeesswari P et al (2012) Design, synthesis, and structure-activity correlations of novel dibenzo[b, d]furan, dibenzo[b, d]thiophene, and N-methylcarbazole clubbed 1,2,3-triazoles as potent inhibitors of *Mycobacterium tuberculosis*. *J Med Chem* 55:3911–3922. doi:[10.1021/jm300125e](https://doi.org/10.1021/jm300125e)
167. Solomon VR, Lee H (2011) Quinoline as a privileged scaffold in cancer drug discovery. *Curr Med Chem* 18:1488–1508. doi:[10.2174/09298671179532.3.2](https://doi.org/10.2174/09298671179532.3.2)
168. Vangapandu S, Jain M, Jain R et al (2004) Ring-substituted quinolines as potential anti-tuberculosis agents. *Bioorg Med Chem* 12:2501–2508. doi:[10.1016/j.bmc.2004.03.045](https://doi.org/10.1016/j.bmc.2004.03.045)
169. Monga V, Nayyar A, Vaitilingam B et al (2004) Ring-substituted quinolines. Part 2: synthesis and antimycobacterial activities of ring-substituted quinolinecarbohydrazide and ring-substituted quinolinecarboxamide analogues. *Bioorg Med Chem* 24:6465–6472. doi:[10.1016/j.bmc.2004.09.017](https://doi.org/10.1016/j.bmc.2004.09.017)
170. Sumangala V, Poojary B, Chidananda N et al (2010) Synthesis and antimicrobial activity of 1,2,3-triazoles containing quinoline moiety. *Arch Pharm Res* 33:1911–1918. doi:[10.1007/s12272-010-1204-3](https://doi.org/10.1007/s12272-010-1204-3)
171. Nayyar A, Patel SR, Shaikh M et al (2009) Synthesis, anti-tuberculosis activity and 3D-QSAR study of amino acid conjugates of 4-(adamantan-1-yl) group containing quinolines. *Eur J Med Chem* 44:2017–2029. doi:[10.1016/j.ejmech.2008.10.004](https://doi.org/10.1016/j.ejmech.2008.10.004)
172. Jain R, Vaitilingam B, Nayyar A et al (2003) Substituted 4-methylquinolines as a new class of anti-tuberculosis agents. *Bioorg Med Chem Lett* 13:1051–1054. doi:[10.1016/S0960-894X\(03\)00074-X](https://doi.org/10.1016/S0960-894X(03)00074-X)
173. Koul A, Dendouga N, Vergauwen K et al (2007) Diarylquinolines target subunit c of mycobacterial ATP synthase. *Nat Chem Biol* 3:323–324. doi:[10.1038/nchembio884](https://doi.org/10.1038/nchembio884)
174. Koul A, Vranckx L, Dendouga N et al (2008) Diarylquinolines are bactericidal for dormant mycobacteria as a result of disturbed ATP homeostasis. *J Biol Chem* 283:25273–25280. doi:[10.1074/jbc.M803899200](https://doi.org/10.1074/jbc.M803899200)
175. Upadhyaya RS, Kulkarni GM, Vasireddy NR et al (2009) Design, synthesis and biological evaluation of novel triazole, urea and thiourea derivatives of quinoline against *Mycobacterium tuberculosis*. *Bioorg Med Chem* 17:4681–4692. doi:[10.1016/j.bmc.2009.04.069](https://doi.org/10.1016/j.bmc.2009.04.069)
176. Kumar KK, Seenivasan P, Kumar V et al (2011) Synthesis of quinoline coupled [1,2,3]-triazoles as a promising class of anti-tuberculosis agent. *Carbohydr Res* 346:2084–2090. doi:[10.1016/j.carres.2011.06.028](https://doi.org/10.1016/j.carres.2011.06.028)
177. Thomas KD, Adhikari AV, Chowdhury IH et al (2011) New quinolin-4-yl-1,2,3-triazoles carrying amides, sulphonamides and amidopiperazines as potential antitubercular agents. *Eur J Med Chem* 46:2503–2512. doi:[10.1016/j.ejmech.2011.03.039](https://doi.org/10.1016/j.ejmech.2011.03.039)

178. Kumar K, Singh P, Kremer L et al (2012) Synthesis and in vitro anti-tubercular evaluation of 1,2,3-triazole tethered β -lactam-ferrocene and β -lactam-ferrocenylchalcone chimeric scaffolds. *Dalton Trans* 41:5778–5781. doi:[10.1039/c2dt30514c](https://doi.org/10.1039/c2dt30514c)
179. Muthukrishnan M, Mujahid M, Yogeewari P et al (2011) Syntheses and biological evaluation of new triazole-spirochromone conjugates as inhibitors of *Mycobacterium tuberculosis*. *Tetrahedron Lett* 52:2387–2389. doi:[10.1016/j.tetlet.2011.02.099](https://doi.org/10.1016/j.tetlet.2011.02.099)
180. Hussain H, Krohn K, Ahmad VU et al (2007) Lapachol: an overview. *Arkivoc Part II*:145–171
181. Fedoryshyn M, Nur-e-Alam M, Zhu L et al (2007) Surprising production of a new urdamycin derivative by *S. fradiae* Delta urdQ/R. *J Biotechnol* 130:32–38. doi:[10.1016/j.jbiotec.2007.02.018](https://doi.org/10.1016/j.jbiotec.2007.02.018)
182. Salas C, Tapia RA, Ciudad K et al (2008) *Trypanosoma cruzi*: activities of lapachol and alpha- and beta-lapachone derivatives against epimastigote and trypomastigote forms. *Bioorg Med Chem* 16:668–674. doi:[10.1016/j.bmc.2007.10.038](https://doi.org/10.1016/j.bmc.2007.10.038)
183. Liu KC, Li J, Sakya S (2004) Synthetic approaches to the 2003 new drugs. *Mini Rev Med Chem* 4:1105–1125. doi:[10.2174/138955704340.9.0](https://doi.org/10.2174/138955704340.9.0)
184. Asche C (2005) Antitumour quinones. *Mini Rev Med Chem* 5:449–467. doi:[10.2174/138955705376.5.6](https://doi.org/10.2174/138955705376.5.6)
185. Santos AF, Ferraz PAL, Pinto AV et al (2000) Molluscicidal activity of 2-hydroxy-3-alkyl-1,4-naphthoquinones and derivatives. *Int J Parasitol* 30:1199–1202. doi:[10.1016/S0020-7519\(00\)00114-4](https://doi.org/10.1016/S0020-7519(00)00114-4)
186. dos Santos AF, Ferraz PAL, de Abreu FC et al (2001) Molluscicidal and trypanocidal activities of lapachol derivatives. *Planta Med* 67:92–93. doi:[10.1055/s-2001-10877](https://doi.org/10.1055/s-2001-10877)
187. Barbosa TP, Camara CA, Silva TMS et al (2005) New 1,2,3,4-tetrahydro-1-aza-anthraquinones and 2-aminoalkyl compounds from norlapachol with molluscicidal activity. *Bioorg Med Chem* 13:6464–6469. doi:[10.1016/j.bmc.2005.06.068](https://doi.org/10.1016/j.bmc.2005.06.068)
188. Teixeira MJ, Almeida YM, Viana JR et al (2001) In vitro and in vivo Leishmanicidal activity of 2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone (lapachol). *Phytother Res* 15:44–48. doi:[10.1002/1099-1573\(200102\)15:1<44::AID-PTR685>3.0.CO;2-1](https://doi.org/10.1002/1099-1573(200102)15:1<44::AID-PTR685>3.0.CO;2-1)
189. Almeida ER, da Silva Filho AA, dos Santos ER et al (1990) Antiinflammatory action of lapachol. *J Ethnopharmacol* 29:239–241. doi:[10.1016/0378-8741\(90\)90061-W](https://doi.org/10.1016/0378-8741(90)90061-W)
190. Gafner S, Wolfender JL, Nianga M et al (1996) Antifungal and antibacterial naphthoquinones from *Newbouldia laevis* roots. *Phytochemistry* 42:1315–1320
191. Pinto CN, Dantas AP, de Moura KCG et al (2000) Chemical reactivity studies with naphthoquinones from *Tabebuia* with anti-trypanosomal efficacy. *Arzneimittelforschung* 50:1120–1128. doi:[10.1055/s-0031-1300337](https://doi.org/10.1055/s-0031-1300337)
192. de Moura KCG, Emery S, Neves-Pinto C et al (2001) Trypanocidal activity of isolated naphthoquinones from *tabebuia* and some heterocyclic derivatives: a review from an interdisciplinary study. *J Braz Chem Soc* 12:325–338. doi:[10.1590/S0103-50532001000300003](https://doi.org/10.1590/S0103-50532001000300003)
193. da Silva Jr EN, Menna-Barreto RFS, Pinto MCFR et al (2008) Naphthoquinoidal [1,2,3]-triazole, a new structural moiety active against *Trypanosoma cruzi*. *Eur J Med Chem* 43:1774–1780. doi:[10.1016/j.ejmech.2007.10.015](https://doi.org/10.1016/j.ejmech.2007.10.015)
194. da Silva Jr EN, de Melo IMM, Diogo EBT (2012) On the search for potential anti-*Trypanosoma cruzi* drugs: Synthesis and biological evaluation of 2-hydroxy-3-methylamino and 1,2,3-triazolic naphthoquinoidal compounds obtained by click chemistry reactions. *Eur J Med Chem* 52:304–312. doi:[10.1016/j.ejmech.2012.03.039](https://doi.org/10.1016/j.ejmech.2012.03.039)
195. Brak K, Doyle PS, McKerrow JH (2008) Identification of a new class of nonpeptidic inhibitors of cruzain. *J Am Chem Soc* 130:6404–6410. doi:[10.1021/ja710254m](https://doi.org/10.1021/ja710254m)
196. Brak K, Kerr ID, Barrett KT (2010) Nonpeptidic tetrafluorophenoxymethyl Ketone Cruzain inhibitors as promising new leads for chagas disease chemotherapy. *J Med Chem* 53:1763–1773. doi:[10.1021/jm901633v](https://doi.org/10.1021/jm901633v)

197. Agustí R, Giorgi ME, de Lederkremer RM (2007) The trans-sialidase from *Trypanosoma cruzi* efficiently transfers alpha-(2->3)-linked N-glycolylneuraminic acid to terminal beta-galactosyl units. *Carbohydr Res* 342:2465–2469. doi:[10.1016/j.carres.2007.07.018](https://doi.org/10.1016/j.carres.2007.07.018)
198. Buschiazio A, Muiá R, Larrieux N et al (2012) *Trypanosoma cruzi* trans-Sialidase in complex with a neutralizing antibody: structure/function studies towards the rational design of inhibitors. *PLoS Pathog* 8:e1002474. doi:[10.1371/journal.ppat.1002474](https://doi.org/10.1371/journal.ppat.1002474)
199. Neres J, Brewer ML, Ratier L et al (2009) Discovery of novel inhibitors of *Trypanosoma cruzi* trans-sialidase from in silico screening. *Bioorg Med Chem Lett* 19:589–596. doi:[10.1016/j.bmcl.2008.12.065](https://doi.org/10.1016/j.bmcl.2008.12.065)
200. Harrison JA, Kartha KP, Fournier EJL et al (2011) *Org Biomol Chem* 9:1653–1660. doi:[10.1039/c0ob00826e](https://doi.org/10.1039/c0ob00826e)
201. Arioka S, Sakagami M, Uematsu R et al (2010) Potent inhibitor scaffold against *Trypanosoma cruzi* trans-sialidase. *Bioorg Med Chem* 18:1633–1640. doi:[10.1016/j.bmc.2009.12.062](https://doi.org/10.1016/j.bmc.2009.12.062)
202. Carvalho I, Andrade P, Campo VL et al (2010) ‘Click chemistry’ synthesis of a library of 1,2,3-triazole-substituted galactose derivatives and their evaluation against *Trypanosoma cruzi* and its cell surface trans-sialidase. *Bioorg Med Chem* 18:2412–2427. doi:[10.1016/j.bmc.2010.02.053](https://doi.org/10.1016/j.bmc.2010.02.053)
203. Goodarzia N, Varshochiana R, Kamaliniia G et al (2013) A review of polysaccharide cytotoxic drug conjugates for cancer therapy. *Carbohydr Polym* 92:1280–1293. doi:[10.1016/j.carbpol.2012.10.036](https://doi.org/10.1016/j.carbpol.2012.10.036)
204. Kamal A, Shankaraiah N, Devaiah V et al (2008) Synthesis of 1,2,3-triazole-linked pyrrolbenzodiazepine conjugates employing click chemistry: DNA-binding affinity and anticancer activity. *Bioorg Med Chem Lett* 18:1468–1473. doi:[10.1016/j.bmcl.2007.12.063](https://doi.org/10.1016/j.bmcl.2007.12.063)
205. Miller MJ, Morasaki GC, Stefely J (2011) Anti-cancer compounds, synthesis thereof, and methods of using same. US Patent 2011/0021574 A1, 27 Jan 2011
206. Fray MJ, Bull DJ, Carr CL et al (2001) Structure-activity relationships of 1,4-dihydro-(1H,4H)-quinoxaline-2,3-diones as N-methyl-D-aspartate (glycine site) receptor antagonists. 1. Heterocyclic substituted 5-alkyl derivatives. *J Med Chem* 24:1951–1962. doi:[10.1021/jm001124p](https://doi.org/10.1021/jm001124p)
207. Kallander LS, Lu Q, Chen W et al (2005) 4-Aryl-1,2,3-triazole: a novel template for a reversible methionine aminopeptidase 2 inhibitor, optimized to inhibit angiogenesis in vivo. *J Med Chem* 48:5644–5647. doi:[10.1021/jm050408c](https://doi.org/10.1021/jm050408c)
208. Li XL, Lin YJ, Wang QQ et al (2011) The novel anti-tumor agents of 4-triazol-1,8-naphthalimides: Synthesis, cytotoxicity, DNA intercalation and photocleavage. *Eur J Med Chem* 46:1274–1279. doi:[10.1016/j.ejmech.2011.01.050](https://doi.org/10.1016/j.ejmech.2011.01.050)
209. Singh P, Raj R, Kumar V et al (2012) 1,2,3-Triazole tethered β -lactam-Chalcone bifunctional hybrids: synthesis and anticancer evaluation. *Eur J Med Chem* 47:594–600. doi:[10.1016/j.ejmech.2011.10.033](https://doi.org/10.1016/j.ejmech.2011.10.033)
210. Kamal A, Prabhakar S, Ramaiah MJ et al (2011) Synthesis and anticancer activity of chalcone-pyrrolbenzodiazepine conjugates linked via 1,2,3-triazole ring side-armed with alkane spacers. *Eur J Med Chem* 46:3820–3831. doi:[10.1016/j.ejmech.2011.05.050](https://doi.org/10.1016/j.ejmech.2011.05.050)
211. Corredor M, Bujons J, Orzáez M (2013) Optimizing the control of apoptosis by amide/triazole isosteric substitution in a constrained peptoid. *Eur J Med Chem* 63:892–896. doi:[10.1016/j.ejmech.2013.03.004](https://doi.org/10.1016/j.ejmech.2013.03.004)
212. Majeed R, Sangwan PL, Chinthakindi PK (2013) Synthesis of 3-O-propargylated betulinic acid and its 1,2,3-triazoles as potential apoptotic agents. *Eur J Med Chem* 63:782–792. doi:[10.1016/j.ejmech.2013.03.028](https://doi.org/10.1016/j.ejmech.2013.03.028)
213. Sanghvi YS, Bhattacharya BK, Kini GD et al (1990) Growth inhibition and induction of cellular differentiation of human myeloid leukemia cells in culture by carbamoyl congeners of ribavirin. *J Med Chem* 33:336–344. doi:[10.1021/jm00163a054](https://doi.org/10.1021/jm00163a054)
214. Gielen M (1996) Tin-based antitumour drugs. *Coord Chem Rev* 151:41–51. doi:[10.1016/S0010-8545\(96\)90193-9](https://doi.org/10.1016/S0010-8545(96)90193-9)

215. Tian L, Sun Y, Li H et al (2005) Synthesis, characterization and biological activity of triorganotin 2-phenyl-1,2,3-triazole-4-carboxylates. *J Inorg Biochem* 99:1646–1652. doi:[10.1016/j.jinorgbio.2005.05.006](https://doi.org/10.1016/j.jinorgbio.2005.05.006)
216. Barnard CFJ (1989) Platinum anti-cancer agents. Twenty years of continuing development. *Platinum Metals Rev* 33:162–167
217. Rosenberg B, Van Camp L, Krigas T (1965) Inhibition of cell division in *Escherichia coli* by electrolysis products from a platinum electrode. *Nature* 205:698. doi:[10.1038.2056.8.0](https://doi.org/10.1038.2056.8.0)
218. Jamieson ER, Lippard SJ (1999) Structure, recognition, and processing of cisplatin-DNA adducts. *Chem Rev* 99:2467–2498. doi:[10.1021/cr980421n](https://doi.org/10.1021/cr980421n)
219. Reedijk J (1999) Why does cisplatin reach Guanine-n7 with competing s-donor ligands available in the cell? *Chem Rev* 99:2499–2510. doi:[10.1021/cr980422f](https://doi.org/10.1021/cr980422f)
220. Fichtinger-Schepman AMJ, van der Veer JL, den Hartog JHJ et al (1985) Adducts of the antitumor drug cis-diamminedichloroplatinum(II) with DNA: formation, identification, and quantitation. *Biochemistry* 24:707–713. doi:[10.1021/bi00324a025](https://doi.org/10.1021/bi00324a025)
221. Pil PM, Lippard SJ (1992) Specific binding of chromosomal protein HMG1 to DNA damaged by the anticancer drug cisplatin. *Science* 256:234–237. doi:[10.1126/science.1566071](https://doi.org/10.1126/science.1566071)
222. Komeda S, Lutz M, Spek AL et al (2002) A novel isomerization on interaction of antitumor-active azole-bridged dinuclear platinum(II) complexes with 9-ethylguanine. Platinum (II) atom migration from N2 to N3 on 1,2,3-triazole. *J Am Chem Soc* 124:4738–4746. doi:[10.1021/ja0168559](https://doi.org/10.1021/ja0168559)
223. Schweinfurth D, Pattacini R, Strobel S et al (2009) New 1,2,3-triazole ligands through click reactions and their palladium and platinum complexes. *Dalton Trans* 9291–9297. doi:[10.1039/b910660j](https://doi.org/10.1039/b910660j)
224. Elamari H, Meganem F, Herscovici J (2011) Chemoselective preparation of disymmetric bistriazoles from bisalkynes. *Tetrahedron Lett* 52:658–660. doi:[10.1016/j.tetlet.2010.11.141](https://doi.org/10.1016/j.tetlet.2010.11.141)
225. Elamari H, Slimi R, Chabot GG et al (2013) Synthesis and in vitro evaluation of potential anticancer activity of mono- and bis-1,2,3-triazole derivatives of bis-alkynes. *Eur J Med Chem* 60:360–364. doi:[10.1016/j.ejmech.2012.12.025](https://doi.org/10.1016/j.ejmech.2012.12.025)
226. Boyle GM (2011) Therapy for metastatic melanoma: an overview and update. *Expert Rev Anticancer Ther* 11:725–737. doi:[10.1586/era.11.25](https://doi.org/10.1586/era.11.25)
227. Griswold DP Jr (1972) Consideration of the subcutaneously implanted B16 melanoma as a screening model for potential anticancer agents. *Cancer Chemother Rep Part 3*:315–324
228. Blanch NM, Chabot GG, Quentin L (2012) In vitro and in vivo biological evaluation of new 4,5-disubstituted 1,2,3-triazoles as cis-constrained analogs of combretastatin A4. *Eur J Med Chem* 54:22–32. doi:[10.1016/j.ejmech.2012.04.017](https://doi.org/10.1016/j.ejmech.2012.04.017)
229. Len C, Boulogne-Merlot AS, Postel D et al (1996) *J Agric Food Chem* 44:2856–2858. doi:[10.1021/jf950751y](https://doi.org/10.1021/jf950751y)
230. Imamura H, Ohtake N, Jona H et al (2001) Dicationic dithiocarbamate carbapenems with anti-MRSA activity. *Bioorg Med Chem* 9:1571–1578. doi:[10.1016/S0968-0896\(01\)00044-X](https://doi.org/10.1016/S0968-0896(01)00044-X)
231. Carta F, Aggarwal M, Maresca A et al (2012) Dithiocarbamates strongly inhibit carbonic anhydrases and show antiglaucoma action in vivo. *J Med Chem* 55:1721–1730. doi:[10.1021/jm300031j](https://doi.org/10.1021/jm300031j)
232. Carta F, Supuran CT (2012) Dithiocarbamates: a new class of carbonic anhydrase inhibitors. Crystallographic and kinetic investigations. *Chem Commun* 48:1868–1870. doi:[10.1039/C2CC16395K](https://doi.org/10.1039/C2CC16395K)
233. Duan YC, Ma YC, Zhang E et al (2013) Design and synthesis of novel 1,2,3-triazole-dithiocarbamate hybrids as potential anticancer agents. *Eur J Med Chem* 62:11–19. doi:[10.1016/j.ejmech.2012.12.046](https://doi.org/10.1016/j.ejmech.2012.12.046)
234. Wang XJ, Xu HW, Guo LL et al (2011) Synthesis and in vitro antitumor activity of new butenolide-containing dithiocarbamates. *Bioorg Med Chem Lett* 21:3074–3077. doi:[10.1016/j.bmcl.2011.03.029](https://doi.org/10.1016/j.bmcl.2011.03.029)

235. Wang XJ, Xu HW, Guo LL et al (2011) Synthesis of various substituted spiro- and bicycletiazolidine-2-thiones by a multicomponent reaction and biological evaluation in vitro. *Heterocycles* 83:1005–1012. doi:[10.3987/COM-11-12147](https://doi.org/10.3987/COM-11-12147)
236. Qian Y, Ma GY, Yang Y et al (2010) Synthesis, molecular modeling and biological evaluation of dithiocarbamates as novel antitubulin agents. *Bioorg Med Chem* 18:43104316. doi:[10.1016/j.bmc.2010.04.091](https://doi.org/10.1016/j.bmc.2010.04.091)
237. Li RD, Zhang X, Li QY et al (2011) Novel EGFR inhibitors prepared by combination of dithiocarbamic acid esters and 4-anilinoquinazolines. *Bioorg Med Chem Lett* 21:3636–3640. doi:[10.1016/j.bmcl.2011.04.096](https://doi.org/10.1016/j.bmcl.2011.04.096)
238. Bacharaju K, Jambula SR, Sivan S et al (2012) Design, synthesis, molecular docking and biological evaluation of new dithiocarbamates substituted benzimidazole and chalcones as possible chemotherapeutic agents. *Bioorg Med Chem Lett* 22:3274–3277. doi:[10.1016/j.bmcl.2012.03.018](https://doi.org/10.1016/j.bmcl.2012.03.018)
239. Macmillan Cancer Support (2013) Fluorouracil (5FU) <http://www.macmillan.org.uk/Cancerinformation/Cancertreatment/Treatmenttypes/Chemotherapy/Individualdrugs/Fluorouracil.aspx>. Accessed 24 Sept 2013
240. Alterio V, Di Fiore A, D'Ambrosio K et al (2012) Multiple binding modes of inhibitors to carbonic anhydrases: how to design specific drugs targeting 15 different isoforms? *Chem Rev* 112:4421–4468. doi:[10.1021/cr200176r](https://doi.org/10.1021/cr200176r)
241. Supuran CT (2008) Carbonic anhydrases: novel therapeutic applications for inhibitors and activators. *Nature Rev Drug Discov* 7:168–181. doi:[10.1038/nrd2467](https://doi.org/10.1038/nrd2467)
242. Neri D, Supuran CT (2011) Interfering with pH regulation in tumours as a therapeutic strategy. *Nature Rev Drug Discov* 10:767–777. doi:[10.1038/nrd3554](https://doi.org/10.1038/nrd3554)
243. Makrecka M, Zalubovskis R, Vavers E et al (2013) Glyoxalase 1 and 2 enzyme inhibitory activity of 6-sulfamoylsaccharin and sulfocoumarin derivatives. *Lett Drug Des Discov* 10:410–414
244. Aggarwal M, McKenna R (2012) Update on carbonic anhydrase inhibitors: a patent review (2008–2011). *Expert Opin Ther Pat* 22:903–915. doi:[10.1517.13543776.2012.707646](https://doi.org/10.1517/13543776.2012.707646)
245. De Simone G, Alterio V, Supuran CT (2013) Exploiting the hydrophobic and hydrophilic binding sites for designing carbonic anhydrase inhibitors. *Expert Opin Drug Discov* 8:793–810. doi:[10.1517.17460441.2013.795145](https://doi.org/10.1517/17460441.2013.795145)
246. Touisni N, Maresca A, McDonald PC et al (2011) Glycosyl coumarin carbonic anhydrase IX and XII inhibitors strongly attenuate the growth of primary breast tumors. *J Med Chem* 54:8271–8277. doi:[10.1021/jm200983e](https://doi.org/10.1021/jm200983e)
247. Davis RA, Vullo D, Maresca A et al (2013) Natural product coumarins that inhibit human carbonic anhydrases. *Bioorg Med Chem* 21:1539–1543. doi:[10.1016/j.bmc.2012.07.021](https://doi.org/10.1016/j.bmc.2012.07.021)
248. Vu H, Pham NB, Quinn RJ (2008) Direct screening of natural product extracts using mass spectrometry. *J Biomol Screen* 13:265. doi:[10.1177.108705710831.7.9](https://doi.org/10.1177/108705710831.7.9)
249. Balboni G, Congiu C, Onnis V et al (2012) Flavones and structurally related 4-chromenones inhibit carbonic anhydrases by a different mechanism of action compared to coumarins. *Bioorg Med Chem Lett* 22:3063–3066. doi:[10.1016/j.bmcl.2012.03.071](https://doi.org/10.1016/j.bmcl.2012.03.071)
250. Maresca A, Temperini C, Vu H et al (2009) Non-Zinc mediated inhibition of carbonic: coumarins are a new class of suicide inhibitors. *J Am Chem Soc* 131:3057–3062. doi:[10.1021/ja809683v](https://doi.org/10.1021/ja809683v)
251. Lou Y, McDonald PC, Oloumi A et al (2011) Targeting tumor hypoxia: suppression of breast tumor growth and metastasis by novel carbonic anhydrase IX inhibitors. *Cancer Res* 71:3364–3376. doi:[10.1158/0008-5472.CAN-10-4261](https://doi.org/10.1158/0008-5472.CAN-10-4261)
252. Tanc M, Carta F, Bozdog M et al (2013) 7-Substituted-sulfocoumarins are isoform-selective, potent carbonic anhydrase II inhibitors. *Bioorg Med Chem* 21:4502–4510. doi:[10.1016/j.bmc.2013.05.032](https://doi.org/10.1016/j.bmc.2013.05.032)
253. Tars K, Vullo D, Kazaks A et al (2013) Sulfocoumarins (1,2-benzoxathiine-2,2-dioxides): a class of potent and isoform-selective inhibitors of tumor-associated carbonic anhydrases. *J Med Chem* 56:293–300. doi:[10.1021/jm301625s](https://doi.org/10.1021/jm301625s)

254. Grandane A, Belyakov S, Trapencieris P et al (2012) Facile synthesis of coumarin bioisosteres-1,2-benzoxathiine 2,2-dioxides. *Tetrahedron* 68:5541–5546. doi:[10.1016/j.tet.2012.04.080](https://doi.org/10.1016/j.tet.2012.04.080)
255. Salmon J, Williams ML, Wu QK et al (2012) Metallocene-based inhibitors of cancer-associated carbonic anhydrase enzymes IX and XII. *J Med Chem* 55:5506–5517. doi:[10.1021/jm300427m](https://doi.org/10.1021/jm300427m)
256. Dwek RA (1996) Glycobiology: toward understanding the function of sugars. *Chem Rev* 96:683–720. doi:[10.1021/cr940283b](https://doi.org/10.1021/cr940283b)
257. Ciocoiu CC, Nikoli N, Nguyen HH et al (2010) Synthesis and dual PPAR α / δ agonist effects of 1,4-disubstituted 1,2,3-triazole analogues of GW 501516. *Eur J Med Chem* 45:3047–3055. doi:[10.1016/j.ejmech.2010.03.035](https://doi.org/10.1016/j.ejmech.2010.03.035)
258. Courageot MP, Frenkiel MP, Dos Santos CD et al (2000) Alfa-Glucosidase inhibitors reduce dengue virus production by affecting the initial steps of virion morphogenesis in the endoplasmic reticulum. *J Virol* 74:564–572. doi:[10.1128/JVI.74.1.564-572.2000](https://doi.org/10.1128/JVI.74.1.564-572.2000)
259. van den Broek LAGM (1997) Azasugars: chemistry and their biological activity as potential anti-HIV drugs. In: Witczak ZJ, Nieforth KA (eds) *Carbohydrates in drug design*. Marcel Dekker, New York, p 471
260. Gross PE, Baker MA, Carver JP et al (1995) Inhibitors of carbohydrate processing: A new class of anticancer agents. *Clin Cancer Res* 1:935–944
261. Stutz A (1999) Iminosugars as glycosidase inhibitors: Nojirimycin and beyond. Wiley-VCH, Weinheim. doi:[10.1002.352760.7.0](https://doi.org/10.1002.352760.7.0)
262. Melo EB, Gomes AS, Carvalho I (2006) α - and β -Glucosidase inhibitors: chemical structure and biological activity. *Tetrahedron* 62:10277–10302. doi:[10.1016/j.tet.2006.08.055](https://doi.org/10.1016/j.tet.2006.08.055)
263. Kumar I, Mir NA, Rode CV et al (2012) Intramolecular Huisgen [3+2] cycloaddition in water: synthesis of fused pyrrolidine-triazoles. *Tetrahedron Asymmetry* 23:225–229. doi:[10.1016/j.tetasy.2012.02.011](https://doi.org/10.1016/j.tetasy.2012.02.011)
264. Valli M, Pivatto M, Danuello A et al (2012) Tropical biodiversity: has it been a potential source of secondary metabolites useful for medicinal chemistry? *Quim Nova* 35:2278–2287. doi:[10.1590/S0100-40422012001100036](https://doi.org/10.1590/S0100-40422012001100036)
265. Moriyama H, Tsukida T, Inoue Y et al (2003) Design, synthesis and evaluation of novel Azasugar-Based MMP/ADAM inhibitors. *Bioorg Med Chem Lett* 13:2741–2744. doi:[10.1016/S0960-894X\(03\)00531-6](https://doi.org/10.1016/S0960-894X(03)00531-6)
266. Medline Plus (2013) Miglitol. <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a601079.html> Accessed 24 Sep 2013
267. Tschamber T, Gessier F, Dubost E et al (2003) Carbohydrate transition state mimics: synthesis of imidazo-pyrrolidinones as potential nectrisine surrogates. *Bioorg Med Chem* 11:3559–3568. doi:[10.1016/S0968-0896\(03\)00402-4](https://doi.org/10.1016/S0968-0896(03)00402-4)
268. Granier T, Panday N, Vasella A (1997) Structure-activity relations for Imidazo-pyridine-type inhibitors of -D-glucosidases. *Helv Chim Acta* 80:979–987. doi:[10.1002/hlca.19970800329](https://doi.org/10.1002/hlca.19970800329)
269. Krulle TM, de la Fuente C, Pickering L et al (1997) Triazole carboxylic acids as anionic sugar mimics? Inhibition of glycogen phosphorylase by a d-glucotriazole carboxylate. *Tetrahedron Asymmetry* 8:3807–3820. doi:[10.1016/S0957-4166\(97\)00561-2](https://doi.org/10.1016/S0957-4166(97)00561-2)
270. Davis BG, Brandstetter TW, Hackett L et al (1999) Tetrazoles of Manno- and Rhamno-Pyranoses: Contrasting inhibition of mannosidases by [4.3.0] but of rhamnosidase by [3.3.0] bicyclic tetrazoles. *Tetrahedron* 55:4489–4500. doi:[10.1016/S0040-4020\(99\)00137-4](https://doi.org/10.1016/S0040-4020(99)00137-4)
271. Périon R, Ferrières V, García-Moreno MI et al (2005) 1,2,3-Triazoles and related glycoconjugates as new glycosidase inhibitors. *Tetrahedron* 61:9118–9128. doi:[10.1016/j.tet.2005.07.033](https://doi.org/10.1016/j.tet.2005.07.033)
272. Sabesan S (2005) New triazole linked carbohydrates useful as glycosidase inhibitors for treating viral infections. US Patent 124563-A1
273. da Rocha DR, Santos WC, Lima ES et al (2012) Synthesis of 1,2,3-triazole glycoconjugates as inhibitors of α -glucosidases. *Carbohydr Res* 350:14–19. doi:[10.1016/j.carres.2011.12.026](https://doi.org/10.1016/j.carres.2011.12.026)

274. Ferreira SB, Sodero ACR, Cardoso MFC (2010) Synthesis, biological activity, and molecular modeling studies of 1,2,3-triazole derivatives of carbohydrates as α -glucosidases inhibitors. *J Med Chem* 53:2364–2375. doi:[10.1021/jm901265h](https://doi.org/10.1021/jm901265h)
275. Senger MR, Gomes LCA, Ferreira SB et al (2012) Kinetics studies on the inhibition mechanism of pancreatic α -Amylase by glycoconjugated 1H-1,2,3-Triazoles: a new class of inhibitors with hypoglycemic activity. *ChemBioChem* 13:1584–1593. doi:[10.1002/cbic.201200272](https://doi.org/10.1002/cbic.201200272)
276. Zhou Y, Zhao Y, O' Boyle KM et al (2008) Hybrid angiogenesis inhibitors: synthesis and biological evaluation of bifunctional compounds based on 1-deoxynojirimycin and aryl-1,2,3-triazoles. *Bioorg Med Chem Lett* 18:954–958. doi:[10.1016/j.bmcl.2007.12.034](https://doi.org/10.1016/j.bmcl.2007.12.034)
277. Diot J, Garcia-Moreno M, Gouin S et al (2009) Multivalent iminosugars to modulate affinity and selectivity for glycosidases. *Org Biomol Chem* 7:357–363. doi:[10.1039/b815408b](https://doi.org/10.1039/b815408b)
278. Park H, Hwang KY, Kim YH et al (2008) Discovery and biological evaluation of novel α -glucosidase inhibitors with in vivo antidiabetic effect. *Bioorg Med Chem Lett* 18:3711–3715. doi:[10.1016/j.bmcl.2008.05.056](https://doi.org/10.1016/j.bmcl.2008.05.056)
279. Potewar TM, Petrova KT, Barros MT (2013) Efficient microwave assisted synthesis of novel 1,2,3-triazole-sucrose derivatives by cycloaddition reaction of sucrose azides and terminal alkynes. *Carbohydr Res* 379:60–67. doi:[10.1016/j.carres.2013.06.017](https://doi.org/10.1016/j.carres.2013.06.017)
280. Dedola S, Nepogodiev SA, Field RA (2007) Recent applications of the CuI-catalysed Huisgen azide-alkyne 1,3-dipolar cycloaddition reaction in carbohydrate chemistry. *Org Biomol Chem* 5:1006–1017. doi:[10.1039/B618048P](https://doi.org/10.1039/B618048P)
281. Dedola S, Hughes DL, Nepogodiev SA et al (2010) Synthesis of α - and β -D-glucopyranosyl triazoles by CuAAC 'click chemistry': reactant tolerance, reaction rate, product structure and glucosidase inhibitory properties. *Carbohydr Res* 345:1123–1134. doi:[10.1016/j.carres.2010.03.041](https://doi.org/10.1016/j.carres.2010.03.041)
282. Tejler J, Skogman F, Leffler H et al (2007) Synthesis of galactose-mimicking 1H-(1,2,3-triazol-1-yl)-mannosides as selective galectin-3 and 9N inhibitors. *Carbohydr Res* 342:1869–1875. doi:[10.1016/j.carres.2007.03.012](https://doi.org/10.1016/j.carres.2007.03.012)
283. Lu WY, Sun XW, Zhu C et al (2010) Expanding the application scope of glycosidases using click chemistry. *Tetrahedron* 66:750–757. doi:[10.1016/j.tet.2009.11.044](https://doi.org/10.1016/j.tet.2009.11.044)
284. Rossi LL, Basu A (2005) Glycosidase inhibition by 1-glycosyl-4-phenyl triazoles. *Bioorg Med Chem Lett* 15:3596–3599. doi:[10.1016/j.bmcl.2005.05.081](https://doi.org/10.1016/j.bmcl.2005.05.081)
285. Goyard D, Praly JP, Vidal S (2012) Synthesis of 5-halogenated 1,2,3-triazoles under stoichiometric Cu(I)-mediated azide-alkyne cycloaddition. *Carbohydr Res* 362:79–83. doi:[10.1016/j.carres.2012.08.014](https://doi.org/10.1016/j.carres.2012.08.014)
286. Asano N (2003) Glycosidase inhibitors: update and perspectives on practical use. *Glycobiology* 13:93–104. doi:[10.1093/glycob/cwg090](https://doi.org/10.1093/glycob/cwg090)
287. Watson AA, Fleet GWJ, Asano N et al (2001) Polyhydroxylated alkaloids - natural occurrence and therapeutic applications. *Phytochemistry* 56:265–295. doi:[10.1016/S0031-9422\(00\)00451-9](https://doi.org/10.1016/S0031-9422(00)00451-9)
288. Gloster TM, Davies GJ (2010) Glycosidase inhibition: assessing mimicry of the transition state. *Org Biomol Chem* 8:305–320. doi:[10.1039/b915870g](https://doi.org/10.1039/b915870g)
289. Kayakiri H, Takase S, Shibata T et al (1989) Structure of kifunensine, a new immunomodulator isolated from an actinomycete. *J Org Chem* 54:4015–4016. doi:[10.1021/jo00278a003](https://doi.org/10.1021/jo00278a003)
290. Cordero FM, Bonanno P, Chioccioli M et al (2011) Diversity-oriented syntheses of 7-substituted lentiginosines. *Tetrahedron* 67:9555–9564. doi:[10.1016/j.tet.2011.10.008](https://doi.org/10.1016/j.tet.2011.10.008)
291. Hamilton TA, Adams DO (1987) Molecular mechanisms of signal transduction in macrophages. *Immunol Today* 8:151–158. doi:[10.1016/0167-5699\(87\)90145-9](https://doi.org/10.1016/0167-5699(87)90145-9)
292. English D, Broxmeyer HE, Gabig TG et al (1988) Temporal adaptation of neutrophil oxidative responsiveness to n-formyl-methionyl-leucyl-phenylalanine. Acceleration by granulocyte-macrophage colony stimulating factor. *J Immunol* 141:2400–2406

293. Lazrek HB, Taourirte M, Oulih T et al (2001) Synthesis and anti-HIV activity of new modified 1,2,3-triazole acyclonucleosides. *Nucleosides Nucleotides Nucleic Acids* 20:1949–1960. doi:[10.1081/NCN-100108325](https://doi.org/10.1081/NCN-100108325)
294. Kiss L, Forró E, Sillanpää R et al (2008) Novel functionalized cispentacin derivatives. Synthesis of 1,2,3-triazole-substituted 2-aminocyclopentane carboxylate stereoisomers. *Tetrahedron Asymmetry* 19:2856–2860. doi:[10.1016/j.tetasy.2008.11.035](https://doi.org/10.1016/j.tetasy.2008.11.035)
295. Wang Q, Li Y, Song C et al (2010) Synthesis and anti-HIV activity of 2'-deoxy-2'-fluoro-4'-C-ethynyl nucleoside analogs. *Bioorg Med Chem Lett* 20:4053–4056. doi:[10.1016/j.bmcl.2010.05.090](https://doi.org/10.1016/j.bmcl.2010.05.090)
296. Guo X, Li Y, Tao L et al (2011) Synthesis and anti-HIV-1 activity of 4-substituted-7-(2'-deoxy-2,3-difluoro-4'-azido-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine analogues. *Bioorg Med Chem Lett* 21:6770–6772. doi:[10.1016/j.bmcl.2011.09.040](https://doi.org/10.1016/j.bmcl.2011.09.040)
297. Wu J, Yu W, Fu L et al (2013) Design, synthesis, and biological evaluation of new 2'-deoxy-2'-fluoro-4'-triazole cytidine nucleosides as potent antiviral agents. *Eur J Med Chem* 63:782–792. doi:[10.1016/j.ejmech.2013.02.042](https://doi.org/10.1016/j.ejmech.2013.02.042)
298. Kumar K, Carrère-Kremer S, Kremer L et al (2013) Azide-alkyne cycloaddition en route towards 1*H*-1,2,3-triazole-tethered β-lactam-ferrocene and β-lactam-ferrocenylchalcone conjugates: synthesis and in vitro anti-tubercular evaluation. *Dalton Trans* 42:1492–1500. doi:[10.1039/c2dt32148c](https://doi.org/10.1039/c2dt32148c)
299. Behbehani H, Ibrahim HM, Makhseed S et al (2011) Applications of 2-arylhydrazononitriles in synthesis: Preparation of new indole containing 1,2,3-triazole, pyrazole and pyrazolo [1,5-*a*]pyrimidine derivatives and evaluation of their antimicrobial activities. *Eur J Med Chem* 46:1813–1820. doi:[10.1016/j.ejmech.2011.02.040](https://doi.org/10.1016/j.ejmech.2011.02.040)
300. Darandale SN, Mulla NA, Pansare DN et al (2013) A novel amalgamation of 1,2,3-triazoles, piperidines and thieno pyridine rings and evaluation of their antifungal activity. *Eur J Med Chem* 65:527–532. doi:[10.1016/j.ejmech.2013.04.045](https://doi.org/10.1016/j.ejmech.2013.04.045)
301. Merino-Montiel P, López O, Álvarez E et al (2012) Synthesis of conformationally-constrained thio(seleno)hydantoins and α-triazolyl lactones from D-arabinose as potential glycosidase inhibitors. *Tetrahedron* 68:4888–4898. doi:[10.1016/j.tet.2012.03.087](https://doi.org/10.1016/j.tet.2012.03.087)
302. Bengtsson C, Lindgren AEG, Uvell H et al (2012) Design, synthesis and evaluation of triazole functionalized ring-fused 2-pyridones as antibacterial agents. *Eur J Med Chem* 54:637–646. doi:[10.1016/j.ejmech.2012.06.018](https://doi.org/10.1016/j.ejmech.2012.06.018)
303. Piotrowska DG, Balzarini J, Glowacka IE (2012) Design, synthesis, antiviral and cytostatic evaluation of novel isoxazolidine nucleotide analogues with a 1,2,3-triazole linker. *Eur J Med Chem* 47:501–509. doi:[10.1016/j.ejmech.2011.11.021](https://doi.org/10.1016/j.ejmech.2011.11.021)
304. Sangaraiah N, Murugan S, Poovan S et al (2012) Facile water promoted synthesis of 1,2,3-triazolyl dihydropyrimidine-2-thione hybrids – highly potent antibacterial agents. *Eur J Med Chem* 58:464–469. doi:[10.1016/j.ejmech.2012.10.029](https://doi.org/10.1016/j.ejmech.2012.10.029)
305. Slámová K, Marhol P, Bezouška K et al (2010) Synthesis and biological activity of glycosyl-1*H*-1,2,3-triazoles. *Bioorg Med Chem Lett* 20:4263–4265. doi:[10.1016/j.bmcl.2010.04.151](https://doi.org/10.1016/j.bmcl.2010.04.151)
306. Nakazawa T, Ohmae T, Fujimuro M et al (2012) Syntheses, molecular structures, and antiviral activities of 1- and 2-(2'-deoxy-D-ribofuranosyl)cyclohepta[d][1,2,3]triazol-6(1*H*)-ones and 1-(2'-deoxy-D-ribofuranosyl)cyclohepta[b]pyrrol-8(1*H*)-one. *Tetrahedron* 68:5368–5374. doi:[10.1016/j.tet.2012.04.109](https://doi.org/10.1016/j.tet.2012.04.109)
307. Jordão AK, Ferreira VF, Souza TML et al (2011) Synthesis and anti-HSV-1 activity of new 1,2,3-triazole derivatives. *Bioorg Med Chem* 19:1860–1865. doi:[10.1016/j.bmc.2011.02.007](https://doi.org/10.1016/j.bmc.2011.02.007)
308. Kim S, Cho SN, Oh T et al (2012) Design and synthesis of 1*H*-1,2,3-triazoles derived from econazole as antitubercular agents. *Bioorg Med Chem Lett* 22:6844–6847. doi:[10.1016/j.bmcl.2012.09.041](https://doi.org/10.1016/j.bmcl.2012.09.041)

Top Heterocycl Chem (2015) 40: 167–210

DOI: 10.1007/7081_2014_123

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Published online: 15 March 2014

Chemistry of 1,2,3-Triazolium Salts

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Abstract 1,2,3-Triazolium salts have been known for a long time. However, their potential as ionic liquids and catalysts was recognized only quite recently. 1,2,3-Triazolium ionic liquids can serve as solvent, as catalyst, as hosts in anion recognition and as components of molecular machines. The major trends in application involve tethering catalytically active species such as (*S*)-proline with triazolium ionic liquids and the use as anion recognizing organocatalysts. Such catalysts are interesting not only due to their recyclability but also because of their outstanding tuneable properties. They can have wide liquid range, thermal stability, tuneable polarity, low flammability, tuneable solubility and low vapour pressure along with ease of separation. The syntheses of 1,2,3- triazolium salts are mainly based on the copper catalysed azide-alkyne cycloaddition (CuAAC) as the most famous click reaction, and subsequent *N*-alkylation of the resulting 1,2,3-triazoles. This synthetic route has the advantage of having four structural units, i.e. the alkyne, the azide, the alkylating agent and the counter anion that can be manipulated in order to tune the properties of the resulting ionic liquid. Unlike the imidazolium ionic liquids 1,2,3-triazolium salts do not have an acidic proton at position 2, which could make them inappropriate for reactions under basic conditions. The low acidity of 1,2,3-triazolium salts in position 4 is exploited in the formation of 1,2,3-triazol-4-ylidene metal complexes with marked catalytic properties.

Keywords 1,2,3-triazolium salt · Alkylation · Catalysis · Click reaction · CuAAC · Ionic liquid

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Abbreviations

Ar	Aryl
Bn	Benzyl
Boc	<i>Tert</i> -butoxycarbonyl
cat	Catalyst
Cbz	Benzyloxycarbonyl
CuAAC	Copper catalysed azide-alkyne cycloaddition
d	Day(s)
DABCO	1,4-diazabicyclo[2.2.2]octane
DCC	<i>N N</i> -dicyclohexylcarbodiimide
DMAP	4-(<i>N N</i> -dimethylamino)pyridine
DMF	<i>N N</i> -dimethylformamide
DMSO	Dimethyl sulphoxide
dr	Diastereomer ratio
ee	Enantiomer excess
equiv	Equivalent(s)
Et	Ethyl
Fmoc	9-Fluorenylmethoxycarbonyl
h	Hour(s)
IL(s)	Ionic liquids
<i>i</i> Pr	Isopropyl
KHMDS	Potassium hexamethyldisilazide potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Me	Methyl
min	Minute(s)
mol	Mole(s)
<i>n</i> Bu	<i>n</i> -butyl
Nu	Nucleophile
Ph	Phenyl
Pr	Propyl
py	Pyridine

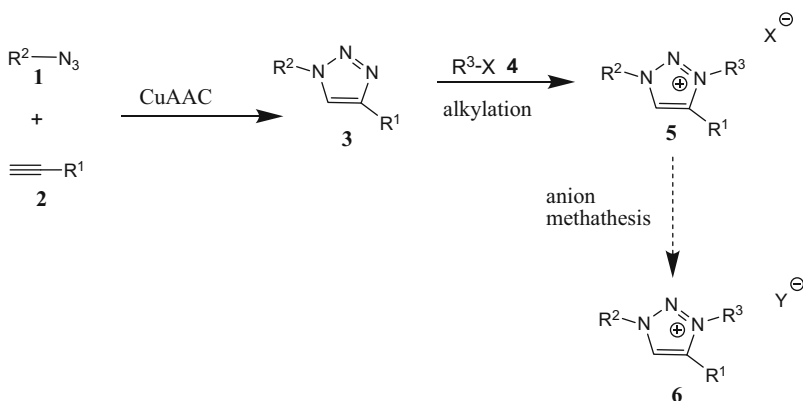
rt	Room temperature
RTILs	Room temperature ionic liquids
s	Second(s)
TBAF	Tetrabutylammonium fluoride
TBDMS	Tert-butyldimethylsilyl
Tf	Trifluoromethanesulphonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethyl- 1,2-ethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl (Tosyl) 4-toluenesulphonyl

1 Introduction

Ionic liquids (ILs) are in most cases salts of large organic cations and inorganic anions with melting point below 100°C. Salts that are liquid at ambient temperature are referred as room temperature ionic liquids (RTILs). The organic cations of ionic liquids mostly contain a positively charged nitrogen atom or sometimes positively charged phosphorous or sulphur atoms on a heterocyclic or acyclic species. Some common ionic liquid cations are quaternary ammonium [1, 2], 1,3-dialkylimidazolium [3–5], pyridinium [6], phosphonium [7], 1,2,3-triazolium [8, 9], 1,2,4-triazolium [10, 11], 1,3-thiazolium [12, 13], sulphonium [14], pyrazolium [15, 16], and oxazolium [17, 18].

ILs have drawn a great deal of attention in the last decade due to their distinctive properties. Among those are exceptionally low vapour pressure, high solvation ability for a variety of compounds, wide liquid range, high polarity, good recyclability, low inflammability, high thermal and electrical stability and good chemical stability (resistance to reduction and oxidation). Additionally, most of the physico-chemical properties of ionic liquids can be tuned to improve or to attain a required physical property. Due to these interesting properties, ILs are considered as designer solvents of the future with a great potential of substituting the commonly used classic volatile organic solvents [19–21].

In the past decade, the research in ionic liquids has been dominated by the ionic liquids based on imidazolium salts [22]. However, recently 1,2,3-triazolium ionic liquids are gaining popularity as phase tags, catalysts and solvents [8, 9, 23, 24]. Here, we provide a comprehensive up-to-date review on the synthesis, properties and applications of 1,2,3-triazolium ILs.



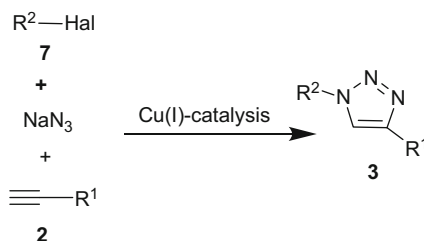
Scheme 1 Major synthetic route towards 1,2,3-triazolium salts

2 Synthesis of 1,2,3-Triazolium Ionic Liquids

The synthesis of 1,3,4-trisubstituted-1,2,3-triazolium ionic liquids involves two basic steps, namely the preparation of the 1,2,3-triazole ring system **3** and its *N*-alkylation. 1,4-Disubstituted 1,2,3-triazoles **3** are easily accessible by the copper(I)-catalysed regioselective [3+2] Huisgen cycloaddition of azides with terminal alkynes (CuAAC) developed by Meldal and Sharpless [25, 26]. This reaction has an extremely wide scope and occurs under mild conditions. The isolation and purification of the products is straightforward [27, 28]. It is important to obtain the 1,2,3-triazole **3** in a pure state before it is transformed into a 1,3,4-trialkyl-1,2,3-triazolium salt (ionic liquid) **5** in the subsequent alkylation step, since purification of the final ionic liquids can be difficult if they are contaminated with other salt-like structures.

The structure of 1,2,3-triazolium-based ionic liquids **5** can be dictated by the CuAAC reaction and by the consecutive alkylation step. Eventually, the anion of the resulting triazolium salt is exchanged by salt metathesis providing salts **6** with a more appropriate anion. The CuAAC is a robust process, which can tolerate a very wide range of functional groups. Thus, functional groups or complete molecular fragments can be introduced into the 1,2,3-triazole ring by choosing appropriate reactants in the CuAAC reaction or by using a functionalized alkylating reagent in the alkylation step (Scheme 1). These possibilities provide a versatile way to assemble a wide scope of molecular structures in the 1,2,3-triazolium ring system to obtain an IL, which is hardly available in the synthesis of other types of ILs.

The copper catalysed [3+2] Huisgen cycloaddition (CuAAC) of a terminal alkyne and an azide produces the 1,4-disubstituted-1,2,3-triazoles **3** with high regioselectivities and yields [28–31]. The copper catalyst can be applied in various forms such as Cu(I) salt or Cu(II) salt together with an in situ reducing agent (sodium ascorbate) [27], Cu(I) salts with triphenylphosphine, with iminopyridine or



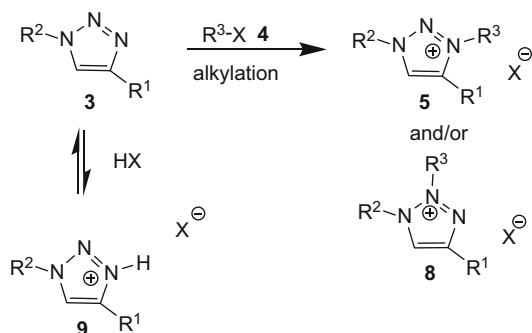
Scheme 2 One-pot synthesis of 1,2,3-triazoles **3** from alkyl halides, sodium azide and terminal alkynes

with mono or multidentate nitrogen ligands, Cu(I) isonitrile complex in water [32], Cu(0) nanoclusters [33, 34] and copper sulphate immobilized on chitosan [35].

There are also alternative methods for obtaining 1,2,3-triazoles from alkynes and azides that have not gained much relevance in the synthesis of 1,2,3-triazolium salts so far. The traditional [3+2] Huisgen cycloaddition reaction of azides with terminal alkynes is performed under thermal conditions in the absence of a copper catalyst. This method, however, results in lower yields and mixtures of regioisomeric 1,4- and 1,5-disubstituted 1,2,3-triazoles, which are difficult to separate. The Cu-free [3+2] dipolar cycloaddition of azides with strained cyclic alkynes such as cyclooctynes runs easier and provides better yields but has structural restrictions and has not gained importance for the synthesis of 1,2,3-triazolium IL [36–39]. Another methodology for copper free [3+2] cycloaddition of terminal alkynes to azide makes use of hydroxide bases and the high acidity of aryl acetylenes. Since this methodology produces 1,5-diaryl substituted 1,2,3-triazoles its scope is restricted [40].

The handling of potentially explosive and dangerous organic azides **1** during the synthesis of 1,4-disubstituted 1,2,3-triazoles **3** can be avoided by means of a one-pot reaction procedure (Scheme 2). The reaction involves an in situ synthesis of the organic azide followed by CuAAC reaction. Various organic azides were in situ synthesized from alkyl halides **7** and used for click reaction. This procedure is efficient for various kinds of alkyl halides **7** and can be applied to iodoarenes, which are nonreactive to nucleophilic substitution by azide under normal conditions. The copper(I) catalyst mediates both the nucleophilic substitution of the halide by an azide and the subsequent [3+2] cycloaddition [41, 42].

The regioselectivity of the [3+2] cycloaddition of azides to alkynes can be altered to the 1,5-disubstituted 1,2,3-triazoles by using other transition metal-based catalysts such as ruthenium [43, 44], palladium [45], or by the use of silyl acetylene or a bromomagnesium acetylide [46, 47]. In a recent approach, the synthesis of 1,5-disubstituted 1,2,3-triazoles was achieved from 1,3,4-trisubstituted 1,2,3-triazolium salts with a 3,4-dimethoxybenzyl protecting group at position 1, which was later removed by means of ammonium nitrate or ceric ammonium nitrate (CAN) [48]. Such 1,2,3-triazoles have, however, not yet been used for triazolium salt formation.

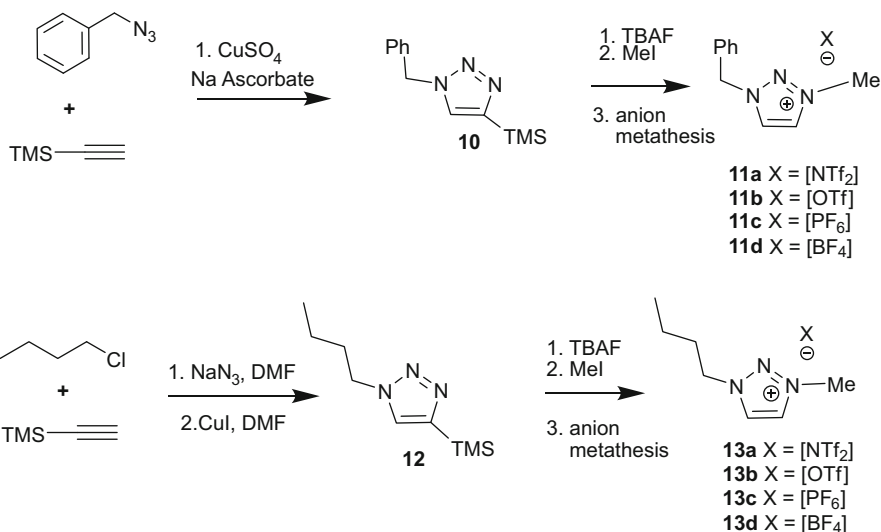


Scheme 3 Regioisomerism in alkylation of 1,2,3-triazoles and protonation of 1,2,3-triazoles

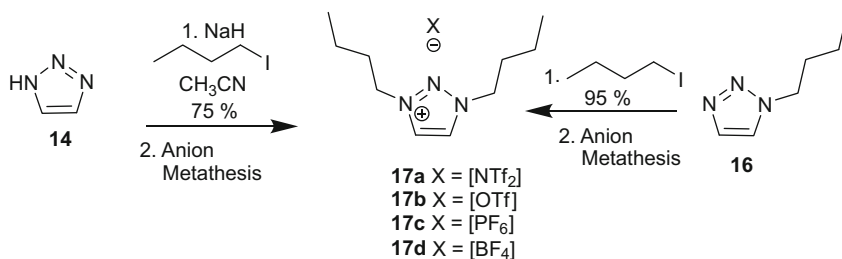
1,4-Disubstituted 1,2,3-triazoles **3** can be transformed into 1,2,3-triazolium salts by alkylation or protonation. The alkylation of 1,2,3-triazoles can furnish 1,3,4- trisubstituted triazolium salt **5** or 1,2,4-trisubstituted triazolium salt **8** depending on the kind of alkylating reagent (Scheme 3). It usually gives high yields. The regioselective 3-alkylation to triazolium salts **5** can be achieved by using soft alkylating agents such as alkyl halides, benzyl halides, allyl halides, sulphates and sulphonates [49]. The treatment of 1,4-disubstituted 1,2,3-triazoles **3** with an inorganic acid can produce a protonated 1,2,3-triazolium salt **9**; however, such salts are unstable in particular under basic conditions and of little use as solvents or catalysts [50].

Among the first triazolium-based ILs, which were utilized as solvent are 1-benzyl-3-methyl-1,2,3-triazolium salts **11**, 1-butyl-3-methyl-1,2,3-triazolium salts **13** and 1,3-dibutyl-1,2,3-triazolium salts **17**. These ILs have substituents only at 1 and 3 positions and are analogues to the 1,3-disubstituted imidazolium ILs. In order to synthesize 1,2,3-triazolium ionic liquids with substituents only at positions 1 and 3 trimethylsilylacetylene can be used as a click reaction substrate and the TMS group is removed from the resulting 1,2,3-triazole by fluoride reagents [51, 52]. Another easy approach towards 1,3-disubstituted-1,2,3-triazolium salts **17** is the alkylation of 1-alkyl-1,2,3-triazole or the alkylation of 1,2,3-triazole with excess of 1-chlorobutane in the presence of a base (Scheme 5) [53].

The 1,3-disubstituted-1,2,3-triazolium salts **11** and **13** were synthesized starting with 1,2,3-triazoles prepared by CuAAC of the corresponding benzyl azide or in situ generated *n*-butyl azide with 1-trimethylsilylacetylene (Scheme 4). The resulting TMS substituted 1,2,3-triazoles **10** and **12** were subjected to TBAF-mediated removal of the TMS group and alkylated with methyl iodide. After anion metathesis with $LiNTf_2$, $KOTf$, $LiPF_6$, or $AgBF_4$ the respective 1,3-disubstituted 1,2,3-triazolium ILs **11** and **13** were obtained in good yields (Scheme 4). The regiochemistry of the *N*-methylation was confirmed by 1D-NOE analysis [52].



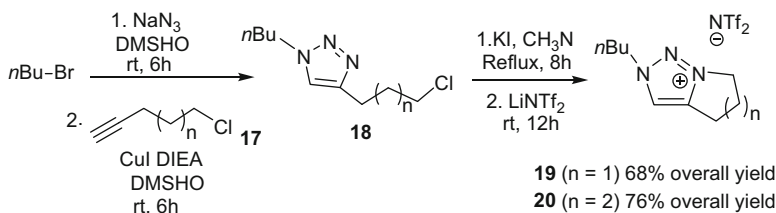
Scheme 4 Synthesis of 1,3-disubstituted 1,2,3-triazolium ionic liquids with unsubstituted positions 4 and 5 using TMS-acetylene



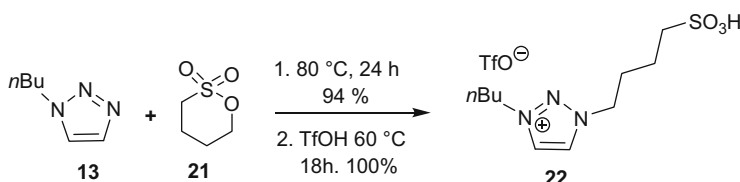
Scheme 5 Synthesis of 1,3-dibutyl-1,2,3-triazolium ionic liquids with unsubstituted positions 4 and 5 by *N*-alkylation

As an alternative access to triazolium salts with unsubstituted positions 4 and 5, *N*-alkylation of 1H-1,2,3-triazole **14** (excess alkylating reagent, after deprotonation by NaH) or 1-substituted 1,2,3-triazole is possible as shown by the synthesis of the 1,3-dibutyl-1,2,3-triazolium ILs **17**. They were obtained after final salt metathesis with LiNTf₂, KOTf, LiPF₆, or AgBF₄ in good yields (Scheme 5).

The bicyclic triazolium ionic liquids [b-3C-tr][NTf₂] **19** and [b-4C-tr][NTf₂] **20** represent another new class of 1,2,3-triazolium-based RTILs investigated as solvents. These ionic liquids were synthesized by in situ generation of *n*-butyl azide from *n*-butyl bromide and sodium azide, followed by CuAAC with 5-chloropentyne or 6-chlorohexyne resulting in 1,2,3-triazoles **18** (Scheme 6). Intramolecular cyclization by *N*-alkylation under Finkelstein reaction conditions and subsequent metathesis of the iodides with LiNTf₂ furnished the desired 1,2,3-triazolium ILs **19** and **20** in good yields.



Scheme 6 Synthesis of bicyclic 1,2,3-triazolium ionic liquids **19** and **20**



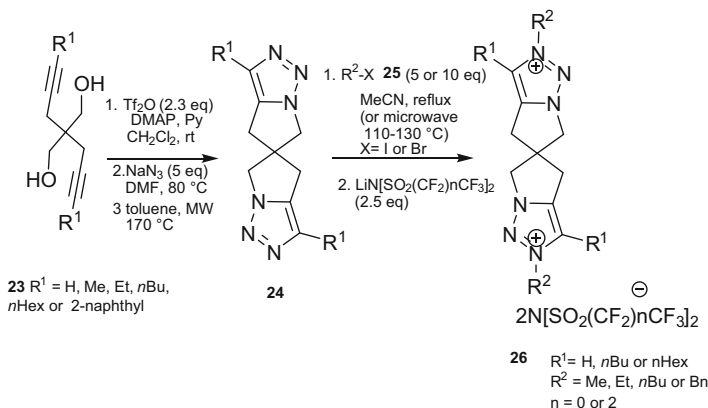
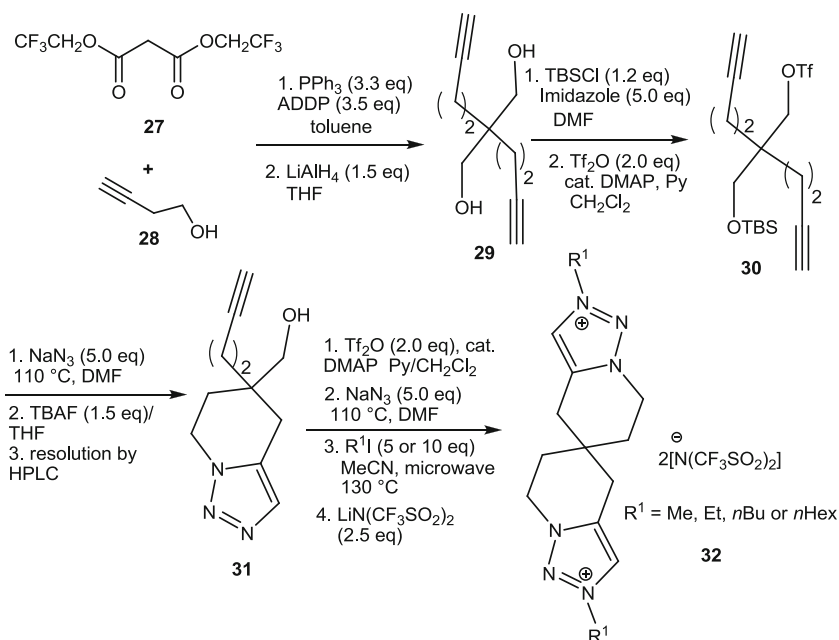
Scheme 7 Synthesis of SO_3H -functionalized 1,2,3-triazolium IL **22**

By the application of the cyclic sulphonate **21** as alkylating reagent a 1,2,3-triazolium IL was obtained with a terminal sulphonic acid group useful as IL-tagged Brønsted acid [54] (Scheme 7).

Unlike imidazolium ILs there are only a few 1,2,3-triazolium-based salts known for potential use as chiral reaction medium (for chiral triazole ILs as organo-catalysts, see Sect. 4.2). The *spiro*-bis(1,2,3-triazolium) salts **26** were developed as potential chiral reaction medium [55, 56]. Their synthesis starts from the ynediol **23**, which was transformed into a diazide via triflation followed by twofold intramolecular Huisgen [3+2] dipolar cycloaddition under microwave conditions. Chiral HPLC was used to separate the enantiomers of the resulting spirotriazoles **24**. Subsequent alkylation and ion metathesis furnished the chiral spirocyclic 1,2,3-triazolium salts **26** (Scheme 8).

Initial investigations of the *spiro*-bis(1,2,3-triazolium) salts **26** and their iodide precursors demonstrated high melting points except the melting point of those with $\text{R}^1 = \text{H}$, $\text{R}^2 = n\text{Bu}$, $n = 0$. The melting point was significantly reduced for *spiro*-bis(1,2,3-triazolium) salts with tetra-alkyl substituents due to their inefficient crystal packing.

Alternatively, enantiopure *spiro*-bis(1,2,3-triazolium) salts with spiro[5.5]undecane skeleton **32** were synthesized in order to obtain chiral 1,2,3-triazolium ILs with lower melting temperature (Scheme 9). The synthesis started with a Mitsunobu reaction of bis(2,2,2-trifluoroethyl) malonate (**27**) with but-3-yn-1-ol **28** followed by reduction with LiAlH_4 to the corresponding diol **29** and selective

**Scheme 8** Synthesis of chiral *spiro*-bis(1,2,3-triazolium) salts**Scheme 9** Synthesis of enantiomerically pure spiro [5.5]undecane

silylation of one of the hydroxy groups with TBS-Cl. The free hydroxyl group of the monosilylated diol was then triflated to result in compound **30**, which was treated with NaN_3 and heated for intramolecular [3+2] dipolar cycloaddition. Deprotection and resolution by chiral HPLC gave either enantiomer of the triazole **31**. This underwent the same sequence to form the second triazole ring. At the end, both triazole rings were *N*-alkylated by alkyl iodides and the iodide replaced by salt

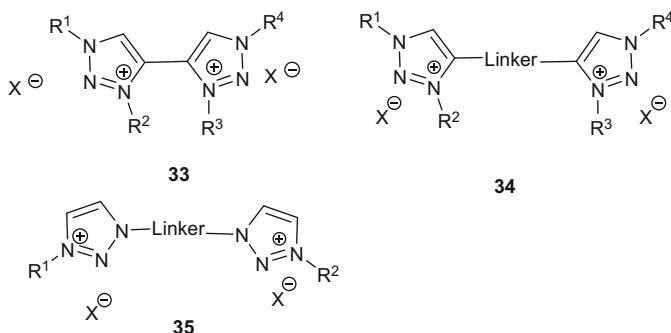


Fig. 1 ILs with two 1,2,3-triazolium units

metathesis providing the bis(1,2,3-triazolium) ILs **32** (Scheme 9). The melting points of **32** were lower than those of triazolium salts **26** while the glass transition temperature (T_g) shows a decrease to less than -11°C . Ionic liquids with T_g as low as -32°C were achieved with the use of long alkyl chains ($R^1 = n\text{Hex}$) and fluoroalkyl counter anions $[\text{N}(\text{SO}_2\text{CF}_3)_2]^-$.

The potential of the *spiro*-triazolium salts in molecular recognition was investigated by using an in situ ^1H NMR of the diastereomeric interaction between a racemic *spiro*-bis(1,2,3-triazolium) salt cation and (*S*)-Mosher's acid chiral anion. The synthetic sequence of CuAAC, alkylation and salt metathesis can also be applied to obtain ILs **33–35** with two 1,2,3-triazolium units (Fig. 1) [57–59].

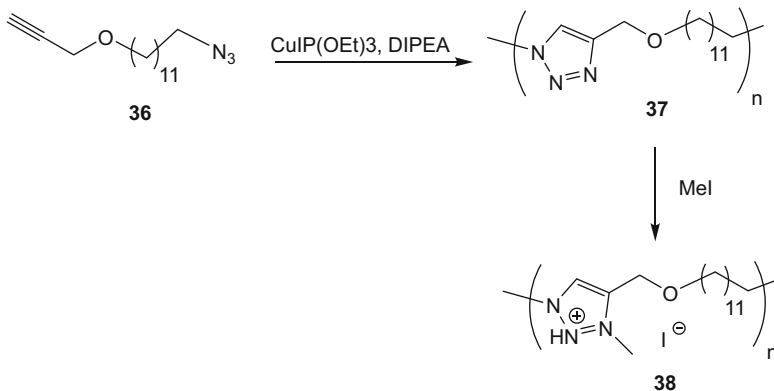
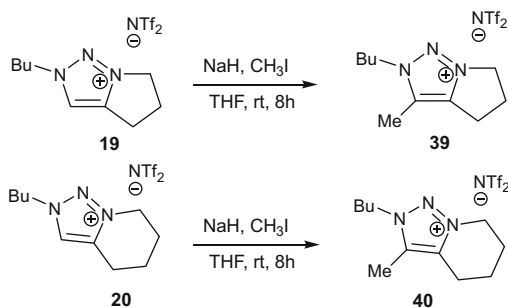
In a similar route also poly(1,2,3-triazolium) ILs can be obtained as demonstrated by the synthesis of the polysalt **38** starting from propargyl 12-azidododecanyl ether **36** (Scheme 10) [60]. Because of their thermodynamic and kinetic stability, they might serve as polymer-electrolytes in fuel cells.

In principle, it is also possible to start with 1,2,3-triazolium salts and to introduce a substituent in position 5 by alkylation as shown with bicyclic 1,2,3-triazolium ionic liquids **19** and **20** (Scheme 11). They were C-alkylated at position-5 after deprotonation with NaH to achieve 1,2,3-triazolium ionic liquids **39** and **40**. This alkylation step was targeted to the prevention of abnormal N-heterocyclic carbene (NHC) formation [61].

Table 1 gives an overview about triazolium ILs, further examples are mentioned in Sect. 4 where applications of 1,2,3-triazolium ILs are discussed.

3 Properties of 1,2,3-Triazolium Ionic Liquids

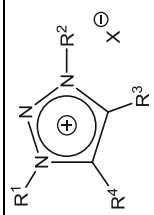
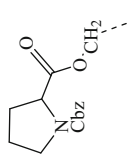
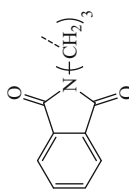
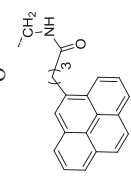
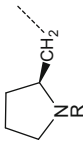
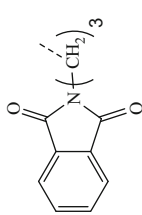
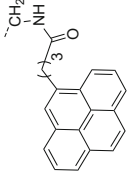
One of the most crucial physical characteristics of ionic liquids is their liquid state at temperatures below 100°C , preferably at ambient temperature. Most 1,3,4-trisubstituted-1,2,3-triazolium salts are found to be liquids at ambient temperature and have lower melting points than their parent 1,4-disubstituted 1,2,3-triazoles.

**Scheme 10** Synthesis of poly(1,2,3-triazolium) ILs**Scheme 11** C-Alkylation of 1,2,3-triazolium ILs **19** and **20**

1,2,3-Triazole-based ionic liquids are usually soluble in polar solvents such as water, methanol, DMF, DMSO and acetonitrile while being immiscible with non-polar solvents such as diethyl ether and hexanes. The 1,2,3-triazolium IL-tagged molecules derived from various amino acids such as proline and lysine also exhibit ionic liquid characteristics in most cases and show similar solubility [8, 42, 65, 74].

Most ILs including 1,2,3-triazolium-based ILs are hygroscopic in nature. The moisture content of ionic liquids plays a significant role in their physicochemical properties and their performance as solvent or catalysts. Due attention must be given to the moisture content (or removal of the moisture) in the ionic liquid before determination of any physicochemical parameter. The hygroscopic nature of ionic liquids depends on its constituents. Some ionic liquids such as those with haloaluminate counter anions may absorb moisture very fast while those with bis (trifluoromethanesulphonyl)imide ($[\text{NTf}_2]^-$) or perfluoroalkylphosphate have less affinity to water but still are hygroscopic. The NTf_2^- salts and the PF_6^- salts are not miscible with H_2O , but the BF_4^- salts are [8, 42, 65, 74].

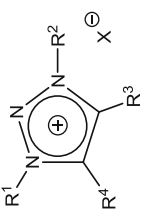
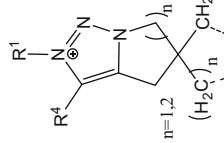
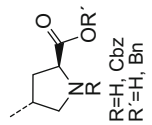
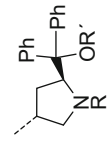
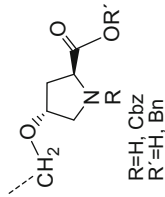
Table 1 Compilation of 1,2,3-triazolium salts 5 and 6

					
R ¹	R ²	R ³	R ⁴	X or Y	Ref
<i>n</i> Bu, Bn, 4-BnOBn	Me	Alkyl, Hydroxyalkyl	H	CF ₃ SO ₃ , I, (MeO)PO ₃ , N(CN) ₂ or BF ₄ , MeSO ₄ , TsO	[8, 42]
Bn	Me		H	I	[8]
4-MeOBn	Et		H	Br	[8]
4-MeOBn	<i>n</i> -Pr		H	I	[8]
	Me	<i>n</i> -Pentyl, Ph	H	I	[8, 62]
	Me		H	I	[8]
Bn, <i>n</i> Bu	Alkyl	H	H	NTf ₂ , OTf, PF ₆ or BF ₄	[52]
Allyl, 3,4-(MeO) ₂ Bn	Me	<i>n</i> -Pentyl	H	I	[42]

4-NCC ₆ H ₄		Et	H	BF ₄	[57]
4- <i>n</i> BuC ₆ H ₄ CH ₂	Me		H	BF ₄	[57]
	Bn, Oct,	Me	H or I	OTf or PF ₆	[42]
<i>n</i> -Octyl	Me	Ph	H	NTf ₂	[63]
R ¹ /R ³	Me	R ¹ /R ³ =	H	BF ₄	[64]
<i>n</i> Bu, Bn	Alkyl	H	H	NTf ₂ , OTf, PF ₆ or BF ₄	[52]
<i>n</i> Bu	R ² /R ³	R ² /R ³ = -(CH ₂) _{<i>n</i>} - <i>n</i> = 3,4	H, Me	NTf ₂	[65]
<i>n</i> Bu	---(CH ₂) ₄ -SO ₃ H	H	H	NTf ₂ , OTf, PF ₆ or BF ₄	[54]

(continued)

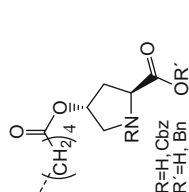
Table 1 (continued)

					
R ¹	R ²	R ³	R ⁴	X or Y	Ref
Alkyl, Bn	R ² /R ³	R ² /R ³ = 	H, <i>n</i> -Bu or <i>n</i> -Hex	N[SO ₂ (CF ₂) _{<i>n</i>} CF ₃] ₂	[55]
	Me	<i>n</i> Bu; H	H	BF ₄ , I CF ₃ SO ₃	[66] [67]
	Me	Alkyl	H	PF ₆	[68]
	Me	<i>n</i> -Dodecyl	H	I, BF ₄	[66]

[69]

 Br, BF_4

H

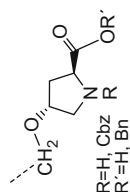
*n*Bu*n*-Bu

[51]

I, BF_4

H

Me



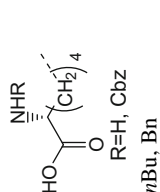
[51]

I, BF_4

H

n-Decyl

Me



[70]

I, BF_4

H

Me

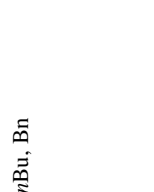


[58]

I, BF_4

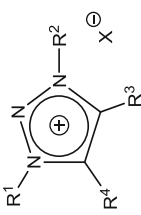
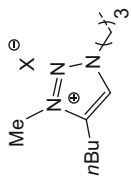
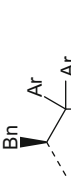
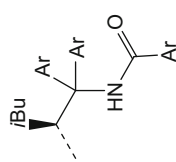
H

Me



(continued)

Table 1 (continued)

					
R ¹	R ²	R ³	R ⁴	X or Y	Ref
	Me	<i>n</i> Bu	H	I, BF ₄	[58]
	Bn, 4-CF ₃ Bn	2-R-C ₆ H ₄ (R = H, Me, Ph), 2-C ₆ H ₅ -4-CF ₃ C ₆ H ₄	H, Me	Br	[71, 72]
	Bn 4-CF ₃ Bn	2-RC ₆ H ₄ (R = Ph, CF ₃ , <i>i</i> Pr), 2-C ₆ H ₅ -4-CF ₃ C ₆ H ₄	H	Br	[73]

The 1,3,4-trisubstituted 1,2,3-triazolium ionic liquids are found to be viscous liquids similar to 1,3-disubstituted imidazolium ionic liquids. The decrease in the cation–anion binding has strong influence on the viscosity of 1,2,3-triazolium-based ILs. Lower viscosity is observed in case of large anions, which can delocalize charge.

Analogous to the melting point of any salt the melting point of an IL is dependent on the anion–cation binding strength. Lower binding results in lower melting point [74, 75]. In the case of 1,2,3-triazolium-based ILs, anions such as halides, triflate or tetrafluoroborate give rise to higher melting points when compared to tosylates [8, 76]. It is a known phenomenon that asymmetrically substituted molecules exhibit lower melting points than symmetric molecules. Likewise, asymmetrically substituted 1,2,3-triazolium as well as imidazolium ionic liquids shows relatively lower melting points, mainly due to an ineffective crystal packing when compared to salts with symmetrical cations [3, 77]. There is also some indication that the substituents at position 1 and 3 of the triazolium ring induce more influence on the phase behaviour of the triazolium salts than the substituents at position 4 [74].

Among the most important physical characteristics of ILs, which render them environmentally benign “green” credentials are their low volatility and their recyclability. In order to be a recyclable solvents or catalysts the ionic liquid must sustain extended stability for the duration of the reaction, while the reaction condition can be mild or harsh such as basic, acidic, oxidizing or reducing at higher temperatures. The thermal stability of 1,2,3-triazolium salts is highly dependent on the type of the counter anion [14, 52]. Contrary to the increase in melting points, strongly binding anions usually reduce the thermal decomposition temperature of the 1,2,3-triazolium-based ILs. ILs with loosely bound cation anion pairs have good thermal stability [18]. ILs can decompose by carbene formation, by deprotonation, by dealkylation of the quaternary nitrogen, by Hoffman elimination or thermally. The thermal, chemical and electrochemical stability of 1,2,3-triazolium-based ionic liquids depends on various factors. However, it is possible to tune the stability of 1,2,3-triazolium ionic liquids by the substituents in the cations and the anions. The unsubstituted 1,2,3-triazolium salts with oxygen-rich anions can be very unstable and possess high explosive nature. Hence, they need to be handled with care.

Differential thermogravimetry (TGA) measurements of some 1,3,4-trisubstituted-1,2,3-triazolium ILs indicated good thermal stability in the range between 200 and 355°C [8, 52]. This value is often lower than that of comparable 1,3-dialkylimidazolium-based ILs, which mostly have thermal decomposition temperature of around 300°C. The thermal stability of 1,2,3-triazolium ILs is strongly dependent on several variables such as the kind of counter-ion and the nature of substituents on the triazolium ring. The 1,2,3-triazolium iodides and triflates show lower thermal stability (near or slightly below 200°C) as compared with respective tosylates, tetrafluoroborates, hexafluorophosphates and bis(trifluoromethylsulphonyl)imides. Relative anion stabilities were suggested to decrease in the order PF_6^- , Tf_2N^- , BF_4^- , TfO^- and I^- . In general, 1,2,3 triazolium ILs show weaker thermal stabilities with the onset of decomposition occurring at about

100 °C when the counter ions are iodide or TfO^- , while salts with bulky anions such as bis(trifluoromethylsulphonyl)amide, hexafluorophosphate and tetrafluoroborate show much higher stabilities [8, 52].

Conductivity measurements of 1,3,4-trisubstituted-1,2,3-triazolium tosylates and triflates revealed values being in a similar order of magnitude as imidazolium ILs with comparable cation sizes but the former have higher conductivity than quaternary ammonium and sulphonium salts [74]. In addition, normal Walden type conductivity was found, which is inversely proportional to the viscosity and arises from migration of charge carriers. Among the 1,2,3-triazolium salts the 1,3,4-trisubstituted-1,2,3-triazolium triflates show higher ionic conductivity than the 1,3,4-trisubstituted-1,2,3-triazolium tosylates. This is due to the smaller size of the triflate, its higher mobility and weaker cation–anion binding.

The electrochemical stability of some 1,2,3-triazolium-based ILs was investigated over a range of -3.2 to $+3.2$ V using a platinum working electrode, silver wire immersed in 0.01 M AgNO_3 in acetonitrile as reference electrode and platinum as counter electrode. The 1,2,3-triazolium ILs exhibited a large electrochemical window of more than 4 V [74]. 1,2,3-Triazolium tosylates possess oxidative stability in the range of 2.5–2.6 V, while corresponding triflates show lower chemical stability in the range of 2.15–2.4 V. 1,2,3-Triazolium cations exhibit better cathodic stability than pyridinium cations but are less stable than quaternary ammonium cations and imidazolium cations. The anions of ILs can be considered to be more stable towards reduction and oxidation than the cations. The cathodic and anodic decomposition potentials of 1,2,3-triazolium ILs are influenced by the cations in a similar manner as 1,3-dialkylimidazolium salts unlike in quaternary ammonium salts where the cathodic limit is governed by reduction of the cation and the anodic limit by oxidation of the anions [74].

1,2,3-Triazolium salts are chemically relatively stable. However, nucleophilic displacement of the alkyl group in position 3 of the triazole ring can occur in some cases.

Properties of ionic liquids often overlooked are their acidity and basicity. IL cations can have Brønsted as well as Lewis acidity whereas anions can have Brønsted and Lewis basicity. Acidity or basicity plays an important role on the stability of ionic liquids additional to their reactivity. Unlike imidazolium salts, 1,2,3-triazolium ionic liquids do not possess acidic hydrogen at position 2 of the triazolium ring and hence are more stable under mildly basic conditions. Therefore, they can serve as innocent reaction medium for base catalysed reactions wherein imidazolium ILs would form carbenes [21, 78]. For example, 1,3,4-trisubstituted-1,2,3-triazolium-based ILs were found to be highly stable under mildly basic conditions such as 0.1 N NaOH while imidazolium ionic liquids show very low stability [74]. Deprotonation at position 4 or 5 of 1,2,3-triazoles is more difficult and was observed with strong bases under H-D exchange conditions in NMR investigations [79]. The formation of transition metal complexes was disclosed in a number of cases recently wherein the triazolium unit was transformed into an N-heterocyclic carbene acting as a 1,2,3-triazol-5-ylidene ligand. This property leads to interesting applications in catalysis of a range of reactions (see Sect. 4.2).

Deuterium isotope exchange experiments for triazolium ionic liquids **19**, **20**, **39** and **40** were conducted under neutral and basic conditions in order to establish the stability of these ILs. ILs **39** and **40** lacking protons in positions 4 and 5 demonstrate very low deuterium isotope exchange after being kept in basic solution for a week. However, triazolium ILs **19** and **20**, which have ionisable protons at carbon-5 underwent deuterium exchange within a few minutes when mixed with the basic deuterium solvent (0.1MKOD in 7:3 mixture of CD₃OD and D₂O) [65].

Under slightly acidic conditions (CD₃OD/D₂O = 7:3, v/v) the ionic liquids **19**, **20**, **39** and **40** did not undergo deuterium isotope exchanges at ambient temperature and were found to be chemically stable for 24 h. However with the elongation of the time to one week the ionic liquids **19** and **20** suffer deuterium isotope exchange of 75% and 11%, respectively, while the ionic liquids **39** and **40** showed no noticeable exchange [65].

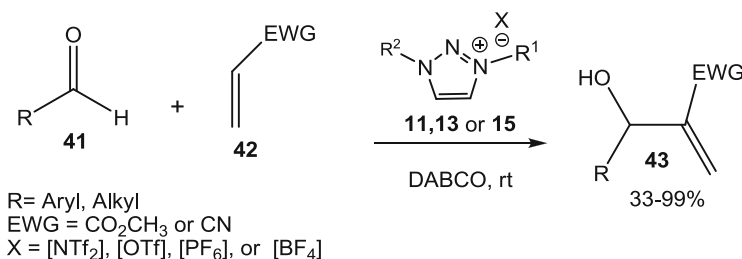
The ionic liquids **19** and **20** have relatively high chemical stability when compared with analogous imidazolium ionic liquids [b-3C-im][NTf₂] and [b-4C-im][NTf₂] under the same basic conditions [80]. This stability makes 1,2,3-triazolium ILs attractive as solvents when bases are applied and for alkaline fuel cell membranes. On the other hand the weak acidity of 1,2,3-triazolium salts allows to form 1,2,3-triazol-5-ylidene complexes with transition metals by deprotonation [81, 82].

4 Application of 1,2,3-Triazolium ILs

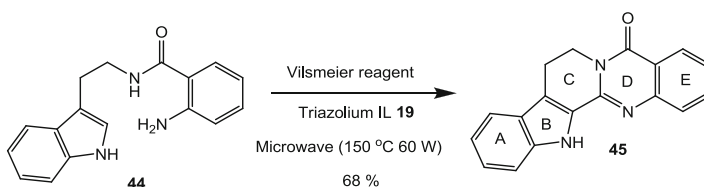
Unlike the imidazolium-based ILs, 1,2,3-triazolium ILs have not yet been commercially produced. This limited availability hampers their utilization as reaction medium. 1,2,3-Triazolium ILs are mainly developed as recyclable designer solvents, catalysts, reagent supports, ionic liquid tags for a specific reaction or as anion recognizing agents or parts of molecular machines.

4.1 Application of 1,2,3-Triazolium Ionic Liquids as Solvents

One of the most interesting properties of 1,2,3-triazolium-based ionic liquids which can be advantageous for application as solvents or catalysts is their tune ability. Various parameters of the triazolium-based ionic liquids such as compatibility with the reaction mixture, polarity, solubility and melting point can be manipulated in order to attain essential characteristics. In addition, various functional groups can also be introduced in the structure of the ILs. For instance, one can introduce a Brønsted acid functional group to the cation of the ionic liquid in order to create an ionic liquid, which can serve as a solvent as well as a catalyst for Brønsted acid catalysed reactions. Similarly, ionic liquids with anions that possess Lewis base characteristics can be synthesized and utilized in a variety of Lewis base catalysed



Scheme 12 Baylis–Hillman reaction in 1,3-disubstituted 1,2,3-triazolium ionic liquids



Scheme 13 Synthesis of rutaecarpine **45** in 1,2,3-triazolium IL **19** as solvent

reactions. These solvent systems are less volatile than conventional solvents and can be recycled by straightforward extraction of the products with non-polar organic solvents, which ultimately increases the efficiency of the solvent and reduces the amount of waste released to the environment and provides economic benefits.

1,3-Dialkyl-1,2,3-triazolium salts were investigated as recyclable solvents for Baylis–Hillman reaction between various aromatic or aliphatic aldehydes and methyl acrylate or acrylonitrile at room temperature in the presence of DABCO (Scheme 12). The 1,2,3-triazolium ILs **11**, **13** and **15** gave the Baylis–Hillman adduct in satisfactory 46% to excellent 96% yields. A comparison made with structurally analogous 1,3-disubstituted imidazolium ILs with identical anions indicated that the 1,3-disubstituted 1,2,3-triazolium ILs provide better yields in shorter reaction times. The weaker performance of the imidazolium ILs results from their low stability in the presence of bases such as DABCO [52, 83]. The 1,2,3-triazolium ionic liquid **13a** was recycled up to four times without a significant loss in yield after extracting the products with diethyl ether.

The bicyclic IL **19** was applied as solvent in the microwave assisted one step production of the C- and D-rings of rutaecarpine. Rutaecarpine, an indolopyridoquinazolinone, is a cytotoxic alkaloid isolated from *Evodiarutaecarpa* and related herbs. The reaction occurred smoothly in the presence of the Vilsmeier reagent to furnish rutaecarpine **45** with 68% isolated yield without any aromatization (Scheme 13) [65].

4.2 Application of 1,2,3-Triazolium Ionic Liquids in Catalysis

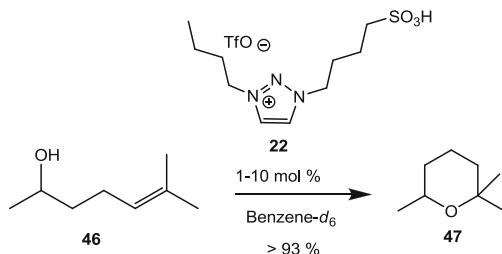
ILs can be applied in catalysis in four different ways. They can serve as solvents, as catalyst, as support for catalytic moieties or as precursors for ligands of catalytic transition metal complexes. Since in the latter case 1,2,3-triazolium salts are transformed into N-heterocyclic carbenes (1,2,3-triazolyl-5-ylidenes) and thus are not any longer ILs; this aspect is only briefly addressed at the end of this chapter. The application of 1,2,3-triazolium ILs as solvents in catalysis or as catalysts has not yet been published. On the other hand, a number of interesting cases were reported, wherein catalytic moieties were linked to 1,2,3-triazolium ILs.

In general, the most common methodology to immobilize catalysts is by means of heterogeneous solid, polymer or gel supports. This methodology offers simplified product isolation by filtration or centrifugation, easy recovery of catalysts, potential for use in continuous processes and enhanced stability when compared to homogenous catalysts. However, such heterogeneous supports often result in low mechanical strength, mass transfer-dependent diffusion, diminished selectivity, reactivity loss, and restricted thermal, chemical and oxidative stability.

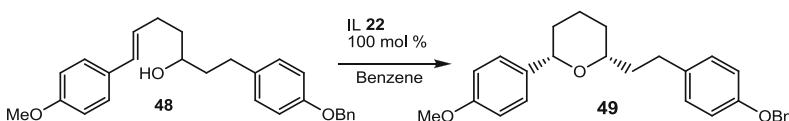
Due to their unique and environmentally benign “green” characteristics, functionalized ionic liquids were implemented as phase tagged organocatalysts. Ionic liquid tagged catalysts combine the advantages of homogeneous catalysis such as higher diffusion, activity and selectivity with the characteristics of heterogeneous catalysts such as ease of separation and reusability. An ionic liquid tag can modify the solubility profile of a catalyst by increasing its partition coefficient in polar solvents and making it insoluble in nonpolar solvents. This makes ionic liquid tagged catalysts pseudohomogeneous and provides a way for recycling by extraction of the reaction products with nonpolar solvents. In addition to an easier recycling, a synergistic improvement of catalytic performance can also result by the tagging of organocatalysts with ionic liquids when compared to non-tagged catalysts [84, 85].

The major pathway of ionic liquid tagging pioneered by Davis and co-workers is covalently linking catalytic functionalities, mainly organocatalysts, to a branch of the ionic liquid cation [86]. There are several examples of imidazolium, ammonium, and 1,2,3-triazolium ionic liquid tagged catalysts [87, 88]. The application of 1,2,3-triazolium ionic liquids as phase tags for catalyst immobilization is a very recent methodology.

The 1,2,3-triazolium IL **22** synthesized by alkylation of the respective 1-butyl-1,2,3-triazole with a cyclic sulphonate contain a strong Brønsted acid at the terminus of one *N*-substituent. It was applied as such in intramolecular hydroalkoxylations of alkenyl alcohols. A 95% yield of the tetrahydropyran **47** was achieved with a catalyst loading as low as 1 mol%. Various kinds of alkenyl alcohols including primary, secondary, aliphatic and aromatic alcohols afford tetrahydropyrans and tetrahydrofurans in this way [54]. The reactions primarily furnished the Markovnikov cyclic ethers regioselectively, which result from the more



Scheme 14 Intramolecular hydroalkoxylation of (±)-6-methyl-5-hepten-2-ol catalysed by IL **22**



Scheme 15 Application of triazolium IL **22** in the synthesis of (±)-centrolobine **49**

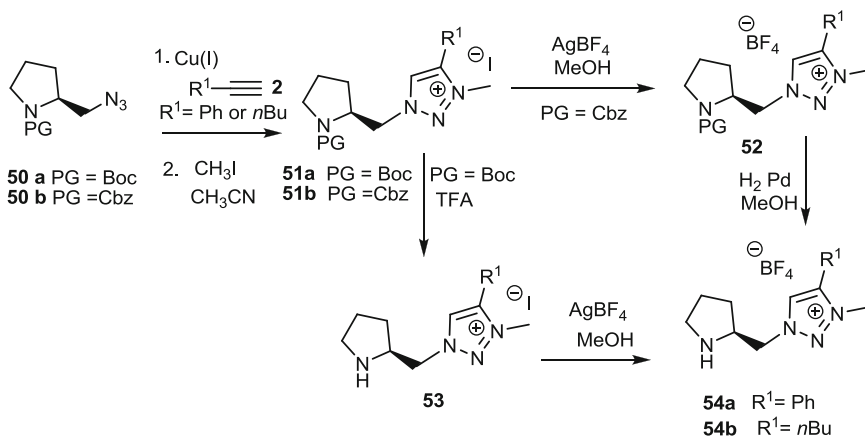
substituted carbocation intermediates. Formation of five membered tetrahydrofuran products is mainly favoured over the six membered tetrahydropyran formation; however, in the presence of an opportunity to form benzylic or tertiary carbocations tetrahydropyrans are favoured products (Scheme 14).

The sulphonic acid functionalized triazolium IL **22** was also investigated in the preparation of (±)-centrolobine **49**, an antibacterial agent isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile*. The product **49** was obtained as the *cis* isomer by cyclization of the alcohol **48** in 82% yield (Scheme 15) [54].

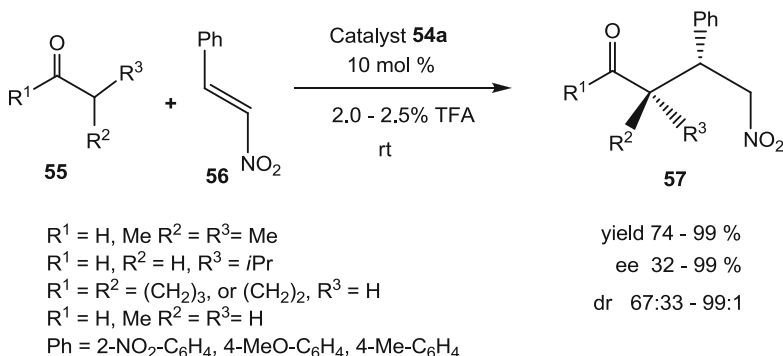
Chiral organocatalysts made from an amino acid derivative tethered to 1,2,3-triazolium ILs have been successfully applied in various organocatalytic reactions [51, 62, 68, 89]. The 1,2,3-triazolium IL tagged pyrrolidines **54** were obtained from (*S*)-prolinol derived azides **50** in a 4-step procedure by first CuAAC with terminal alkynes and then *N*-alkylation providing the triazolium iodides **51**, which were transformed into the triazolium tetrafluoroborates **54** by salt metathesis with Ag-tetrafluoroborate and deprotection (Scheme 16) [62].

It is worth mentioning that hydrogenative removal of the Cbz protecting group from the iodide **51b** failed probably due to poisoning of the Pd catalyst while it occurred smoothly at the tetrafluoroborate **52**.

The 1,2,3-triazolium-tagged pyrrolidines **54** were applied in asymmetric Michael addition of various unmodified aldehydes and ketones **55** to *trans*-β-nitrostyrenes **56**. It turned out that the substituent R (*n*-butyl or phenyl) in the triazolium ring does not seem to have an influence on the outcome of the reaction. The 1,2,3-triazolium IL **54a** was found to be a very efficient recyclable catalyst. It gave excellent enantioselectivities up to 99% and diastereoselectivities up to 99:1 with yields reaching 98%. The reactions were undertaken with 10 mol%



Scheme 16 Synthesis of 1,2,3-triazolium ionic liquid-tagged chiral pyrrolidinemethyl organocatalysts **54a** and **54b**



Scheme 17 Application of the triazolium catalyst **54a** in Michael addition of carbonyl compounds to *trans*- β -nitrostyrene

of the catalyst in the presence of 2.0–2.5% TFA additive and the carbonyl component was used in excess as solvent (Scheme 17). β -Nitrostyrenes comprising electron donating (4-MeO, 4-Me) or electron withdrawing (2-NO₂) groups in the aryl ring gave rise to excellent yields and diastereoselectivities but with somewhat lower enantioselectivities (83–90%).

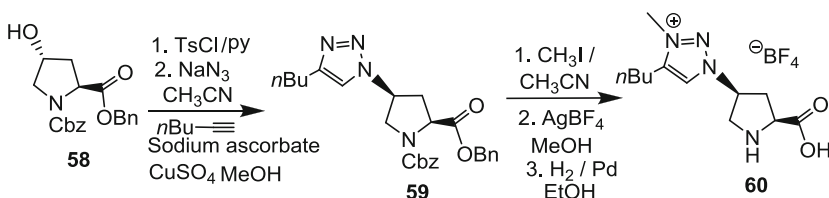
Among the various carbonyl compounds used as substrates for the Michael addition to *trans*- β -nitrostyrene, acetone furnished 85% yield and low (52%) enantioselectivity in a shorter reaction period. This result resembles the one found by Yan et al. using a similar 1,2,3-triazole catalyst [90]. Cyclopentanone was often reported to give low selectivity for non-immobilized catalysts under Michael addition to *trans*- β -nitrostyrenes. This was also observed with the 1,2,3-triazolium IL tagged catalysts **54** in which a low (67:33) diastereoselectivity and

82% enantioselectivity was achieved. Furthermore, catalysts **54** catalysed efficiently the reaction between aldehydes and β -nitrostyrene. This reaction is known to have complications due to the relatively higher reactivity of aldehydes and their tendency to undergo detrimental intermolecular self-aldol reactions [91]. 1,2,3-Triazolium IL-based catalysts **54** furnished high yields, high diastereoselectivities but lower and less convincing enantioselectivities. As checked for the Michael addition of cyclohexanone to *trans*- β -nitrostyrene, 1,2,3-triazolium IL catalysts could easily be recycled by extraction of the reaction products with diethyl ether and combining the remainder with a fresh batch of reactants. The triazolium iodide catalyst **53** ($R^1 = \text{Ph}$) was recyclable up to four times. The products exhibited constantly high diastereoselectivities (higher than 93:7). However, the enantioselectivity dropped from 99% in the first run to 58% in the fourth run. The yield also showed decline from 98% in the first run to 74% in the fourth run. However, the recyclability of the catalysts was improved after anion metathesis. Catalysts **54** with the tetrafluoroborate counter anion showed improved recyclability as compared with their iodide counterparts. Catalyst **54a** was recycled four times without any drop in the yield or enantioselectivity of the product [92]. When the amount of the catalyst **53** ($R^1 = \text{Ph}$) was reduced to 5 mol% the enantioselectivity decreased to 82% and the reaction required slightly longer time to complete. However, the yield (>95%) and the diastereoselectivity (97:3) remained high.

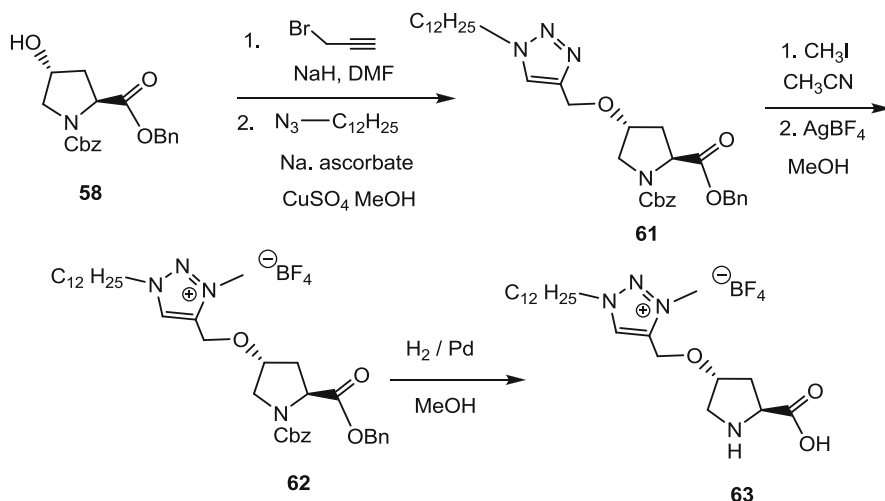
Proline and its derivatives belong to the most versatile and frequently used organocatalyst systems. One of the methods of tagging proline with 1,2,3-triazolium ILs involves the use of a 4-hydroxy substituent on (*S*)-proline while keeping the 2-carboxylic acid functional group intact, eventually via intermediate protection or transforming the latter into a diphenylhydroxymethyl moiety.

One way to tag *trans*-4-hydroxy-(*S*)-proline with 1,2,3-triazolium ionic liquid was found by converting the 4-hydroxy group into an azido or a terminal alkyne derivative for CuAAC reaction. Alternatively, the 4-hydroxy group can be transformed into a leaving group for nucleophilic substitution by a 1,2,3-triazole forming a triazolium salt. In the first strategy, the *N*-Cbz protected-4-hydroxyproline benzyl ester **58** was treated with tosyl chloride to obtain a tosylate substituted precursor, which can easily undergo nucleophilic substitution by sodium azide resulting in the 4-*cis* azido substituted product. Click reaction of this azide derivative with 1-hexyne furnished the 1,2,3-triazole **59** in good yield. The 1,2,3-triazole derivative was alkylated by methyl iodide and subjected to salt metathesis with silver tetrafluoroborate (AgBF_4). The resulting 1,2,3-triazolium IL derivative was submitted to palladium catalysed hydrogenation (H_2/Pd) for a simultaneous deprotection of the Cbz and the benzyl ester group to furnish the target catalyst **60** in excellent yield (Scheme 18) [66].

The 4-hydroxy group of *N*-Cbz protected *trans*-4-hydroxy-(*S*)-proline **58** can also be used as a propargyl component in CuAAC click reaction. In this methodology the synthesis of 1,2,3-triazole tagged catalyst begins by a base catalysed introduction of the propargyl group with propargyl bromide. Subsequent CuAAC reaction with 1-azidododecane furnished the triazole **61** in 71% yield. Alkylation with methyl iodide and anion metathesis led to the catalyst precursor **62**. Final



Scheme 18 1,2,3-Triazole tagging of (*S*)-proline via a 4-hydroxy group

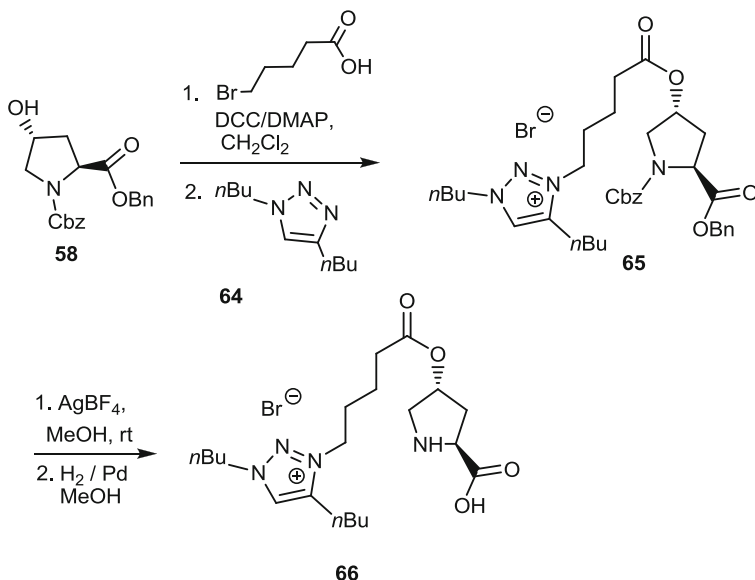


Scheme 19 Synthesis of 1,2,3-triazolium tagged catalyst from propargylated *trans*-4-hydroxy *S*-proline

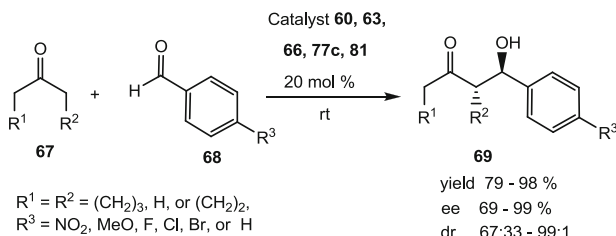
double deprotection of both the benzyl and Cbz group by catalytic hydrogenation gave the desired catalyst **63** (Scheme 19) [66].

Another 1,2,3-triazolium ionic liquid tagged catalyst **66** obtained from diprotected *trans*-4-hydroxy proline **58** utilizes an ester linkage formed by reaction of *trans*-4-hydroxy proline with 5-bromovaleric acid. The resulting bromo substituted product was further used as alkylating reagent for 1,4-di(*n*-butyl)-1,2,3-triazole **64**. Anion metathesis of the resulting triazolium bromide **65** with AgBF₄ followed by catalytic hydrogenation furnished the target catalyst **66** (Scheme 20) [66].

Catalysts **60** and **63** were found to be highly efficient in direct aldol reactions. The reaction of various aromatic aldehydes with acetone, cyclohexanone, or cyclopentanone catalysed by catalyst **60** furnished high yields (>84%) and enantioselectivities (>76%). Both aromatic aldehydes substituted with electron withdrawing 4-nitro- and electron donating 4-methoxy group furnished excellent yields (>91%) and enantioselectivities (> 98%) as well as diastereoselectivities (>97:3). Variation of the substituent on the aromatic ring of the aldehyde from the



Scheme 20 Synthesis of 1,2,3-triazolium ionic liquid tagged catalyst **66**. Counter anion of **66** must be BF_4^-

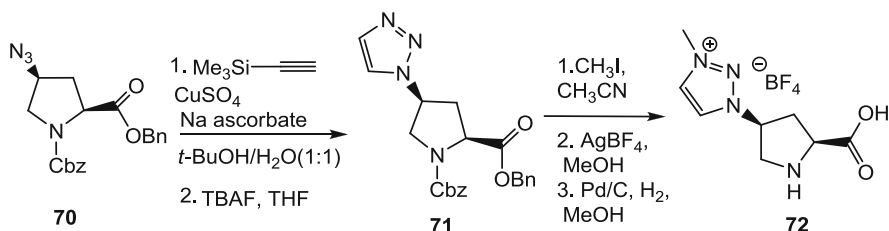


Scheme 21 Aldol reactions catalysed by 1,2,3-triazolium tagged catalysts **60**, **63**, **66**, **77c**, **81**

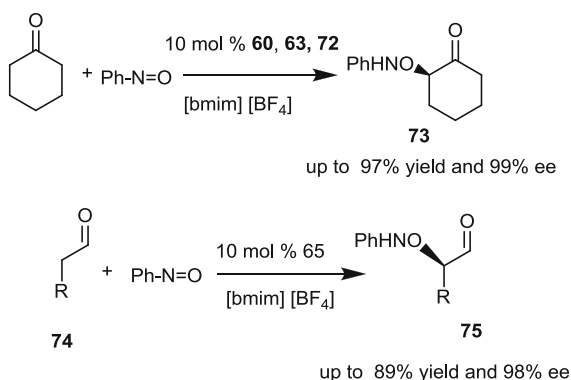
electron withdrawing nitro group to the electron donating methoxy group did not influence the outcome of the reaction. Catalysts **60**, **63** and **66** furnished better enantioselectivities for acetone as enol component as compared to other catalysts [**66**] (Scheme 21).

Catalyst **60** was recycled by extraction of the reaction products with diethyl ether or cyclohexane. The latter gave better results in recycling providing 88% yield and 68% ee in the fifth cycle. Performing the aldol reaction catalysed by **60** in [bmim][BF_4] ionic liquid leads to detrimental effects in recycling [**66**].

In order to obtain proline with a 1,2,3-triazolium tag, which has no substituent at position 4, TMS-ethyne was applied as alkyne component in CuAAC with 4-azidoproline derivative **70** (Scheme 22). The TMS-group was removed by tetrabutyl ammonium fluoride and the resulting 1,2,3-triazole derivative **71** alkylated by methyl iodide and subjected to salt metathesis with silver



Scheme 22 Synthesis of proline tagged with 4-unsubstituted 1,2,3-triazolium **II**



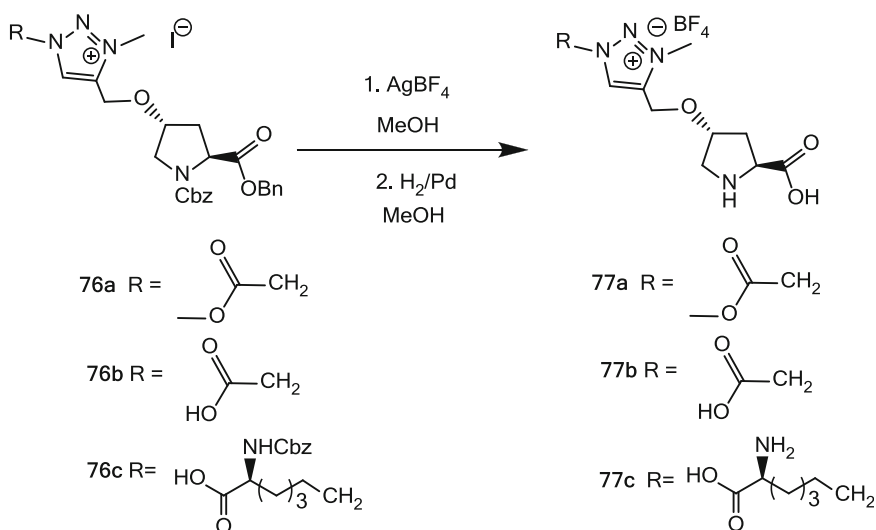
Scheme 23 Application of triazolium tagged catalysts in α -aminoxylation of carbonyl compounds in $[\text{bmim}][\text{BF}_4]$ solvent

tetrafluoroborate (AgBF_4). Deprotection by palladium catalysed hydrogenation provided the target catalyst **72** (Scheme 22) [66]. This strategy was also used by Jeong and Ryu [52] in order to synthesize 1,3-dialkyl-1,2,3-triazolium ionic liquid solvents independently of our work.

Catalyst **72**, which lacks a substituent at position 4 of the 1,2,3-triazole ring was investigated in asymmetric α -aminoxylation using $[\text{bmim}][\text{BF}_4]$ ionic liquid. It showed lower efficiency (82% yield and 78% ee) when compared to catalysts with alkyl substituent at position 4 such as catalyst **60** or **63** providing excellent yields and enantioselectivities (Scheme 23) [67]. In these cases [67] even better results were obtained than with untaged (*S*)-proline and its derivatives.

The potential of catalyst **63** was also investigated in Michael addition of cyclohexanone, cyclopentanone and acetone to various *trans*- β -nitrostyrenes similar to the application of catalyst **60** (Scheme 21). The Michael addition products were obtained with high yield and diastereoselectivities but with somewhat lower enantioselectivities [66].

The flexibility of the 2-step synthesis of 1,2,3-triazolium salts was further explored to attach two potentially catalytically active moieties to the triazole ring (Scheme 24). Following analogous reaction steps as Scheme 19, azidoacetic acid, methyl azidoacetate or a lysine-derived azide were applied as azido component to furnish



Scheme 24 Synthesis of 1,2,3-triazolium IL catalysts with additional functional groups

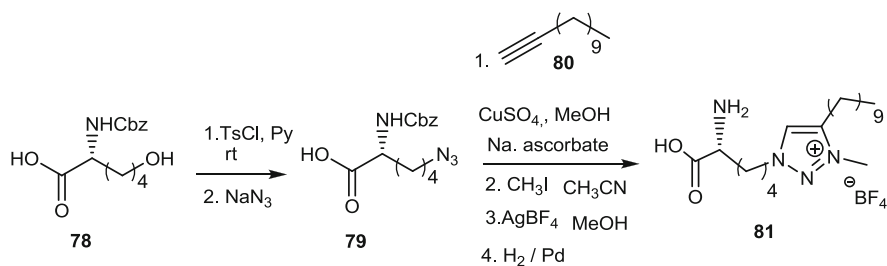
the 1,2,3-triazolium iodides **76**. Anion metathesis with silver tetrafluoroborate and palladium catalysed reductive hydrogenation gave the 1,2,3-triazolium tetrafluoroborates **77** where respective functional groups are found at position 1 in addition to the hydroxyproline moiety at position 4 [67].

However, these additional functionalities found in the 1,2,3-triazolium-tagged catalysts **77a,b** exhibited a detrimental effect in catalysis of the aminooxylation of cyclohexanone with nitrosobenzene in [bmim][BF₄] leading to low enantioselectivities [51, 93].

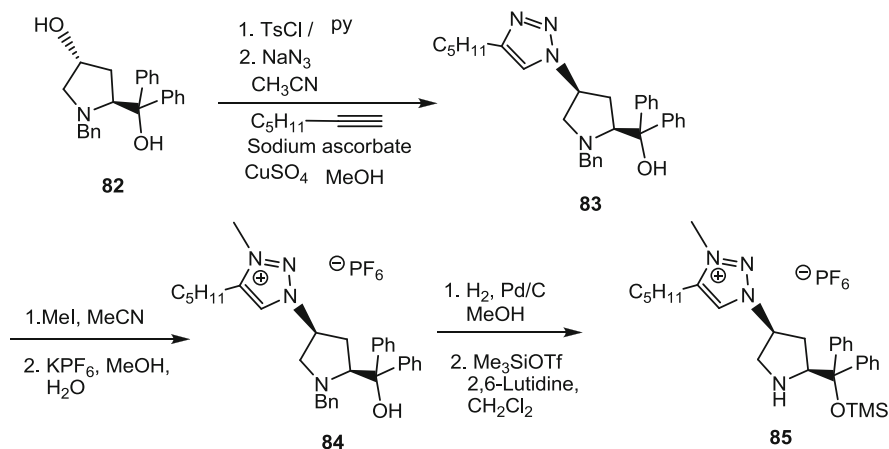
On the other hand, the application of the catalyst **77c** in 20 mol% furnished good yields (87–95%), diastereoselectivities (65:35–99:1) and enantioselectivities (82–98%) in aldol reactions (Scheme 21) [51]. Interestingly, the prolongation of the reaction time from 24 h to 96 h resulted in the decrease of the diastereoselectivities and chemical yields. Reducing the amount of organocatalyst from 20 mol% to 10 and 5 mol% did not affect the diastereoselectivity but resulted in diminished enantioselectivities and yields.

The recyclability of the 1,2,3-triazolium tagged organocatalyst **77c** was investigated by extracting the aldol products with diethyl ether and combining the remainder with a fresh batch of reactants. It was found that the rate of the reaction decreased with each recycling. However, the enantioselectivity remained persistently high (> 90%) for consecutive five cycles. The diastereoselectivities decreased from 98:2 in the first run to 80:20 in the fifth run [51].

A potential lysine derived organocatalyst **81** without an additional proline moiety was obtained from 2-(benzyloxycarbonylamino)-6-hydroxyhexanoic acid **78** by replacing the terminal hydroxyl group with azide followed by the usual protocol: CuAAC with dodecyne, methylation, salt metathesis and deprotection



Scheme 25 Synthesis of a 1,2,3-triazolium tagged *L*-lysine derivative



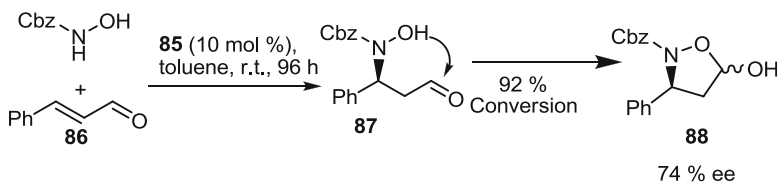
Scheme 26 Synthesis of α, α -diphenylprolinol derived ionic liquid-tagged catalyst

(Scheme 25) [51]. It performed very well as catalyst in aldol reactions (Scheme 21) and gave even better results than the dual 1,2,3-triazolium catalyst **77c**.

As another type of well-known organocatalysts, a Jørgensen type catalyst was tagged with a 1,2,3-triazolium salt. Instead of *trans*-4-hydroxyproline used for prolinyl-1,2,3-triazolium salts the corresponding diphenylcarbinol **82** was transformed into a *cis*-4-azidoderivative and submitted to the general reaction sequence to 1,2,3-triazolium salts by CuAAC, methylation, salt metathesis to give the hexafluorophosphate **85** (Scheme 26) [68].

Catalyst **85** was applied in a domino reaction of cinnamaldehyde with *N*-Cbz protected hydroxyl amine involving an aza-Michael addition followed by an intramolecular acetalization. The product was obtained with 92% conversion and 74% enantioselectivity (Scheme 27) [68].

The methodology of tagging organocatalysts with 1,2,3-triazolium-based ILs was further extended to the area of hydrogen bonding catalysis [70]. $\alpha, \alpha, \alpha', \alpha'$ -Tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL) and substituted analogues showed an outstanding performance in hydrogen bonding catalysis, as bidentate alkoxide ligands and as chiral auxiliaries [94, 95]. 1,2,3-Triazolium tagged TADDOLs

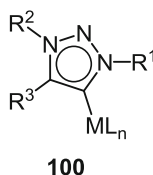


Scheme 27 Domino reaction between *trans*-cinnamaldehyde and *N*-Cbz- hydroxylamine catalysed by ionic liquid catalyst **85**

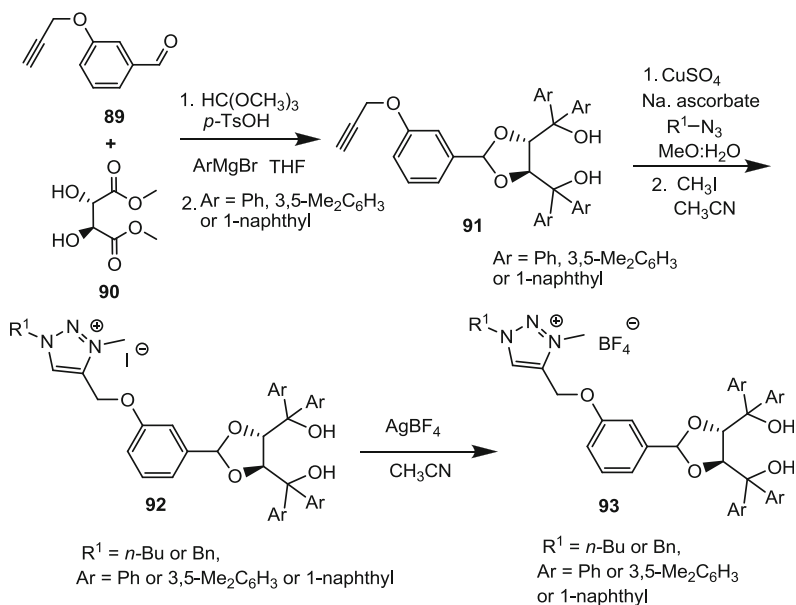
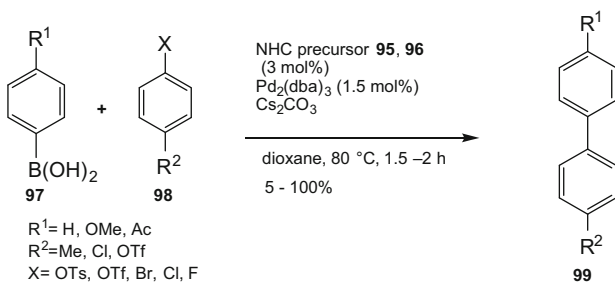
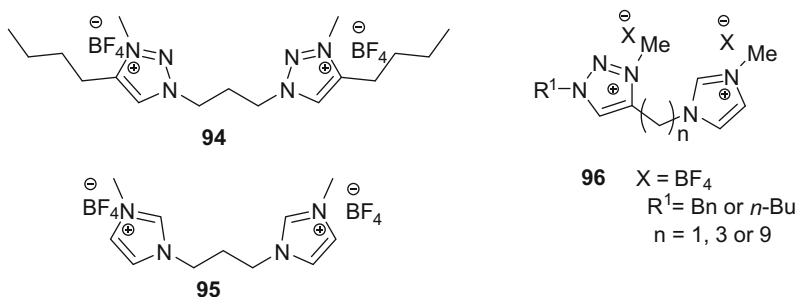
were synthesized starting from 3-propargyloxybenzaldehyde **89** and dimethyl L-(+)-tartrate **90**. After building up the TADDOL skeleton **91** the 1,2,3-triazolium salt unit was established in the usual way (CuAAC, methylation, salt metathesis) providing the 1,2,3-triazolium tetrafluoroborate tagged TADDOLs **93** [70, 92]. These systems were tested in hetero-Diels Alder reactions between activated dienes (Rawal's and Bras-sard's diene) and benzaldehyde but unfortunately showed a weaker performance in terms of yields and enantioselectivity than the untagged parent systems (Scheme 28).

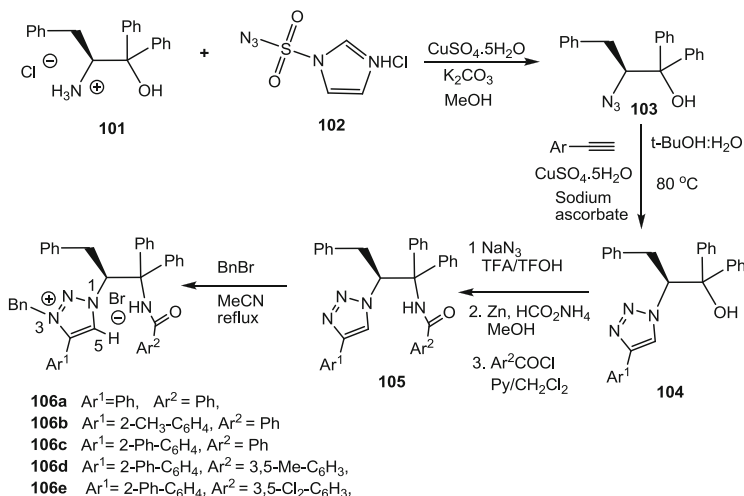
The 1,2,3-triazolium moiety was also used as IL tag for N-heterocyclic carbenes in metal complexes [51]. Thus the 1-imidazolium- ω -1,2,3-triazolium alkanes **96** were synthesized starting from a 1-alkynylimidazole by CuAAC with an azide, double methylation and salt metathesis. It was added to Pd₂(dba)₃ in the presence of cesium carbonate forming an imidazolylidene ligand. The resulting complex performed very well in Suzuki-Miyaura coupling (Scheme 29). Its performance was better than when symmetric 1, ω -diimidazolium **95** or 1, ω -ditriazoliumalkanes **94** was used as precursors for NHC-ligands (Fig. 2).

In this context, it has to be mentioned that also 1,2,3-triazolium salts themselves can act as precursors of NHC-ligands for transition metals by deprotonation of position 5 [61, 96–98]. In fact, recent results proved that 1,2,3-triazol-5-ylidene palladium and copper complexes **100** formed from 1,2,3-triazolium salts are efficient catalysts for a number of reactions, such as Suzuki–Miyaura coupling [58, 99–101] Heck–Mizoroki–Heck olefination [102, 103], Sonogashira reaction [102] and CuAAC, respectively [104–106]. The Pd triazol-5-ylidene complexes **100** can even perform better than Pd-imidazolylidene complexes in some cases [99]. Iron and magnesium 1,2,3-triazolylidene complexes **100** served as catalysts in allylation of various nucleophiles [107, 108].



1,2,3-Triazol-5-ylidene complexes **100** with iridium or ruthenium have found application as catalysts in olefin metathesis [109], water oxidation [110–112], as

**Scheme 28** Synthesis of TADDOL catalysts tagged with 1,2,3-triazolium salts**Scheme 29** Suzuki–Miyaura cross-coupling reaction catalysed by catalyst **95**, **96****Fig. 2** IL tag for N-heterocyclic carbenes



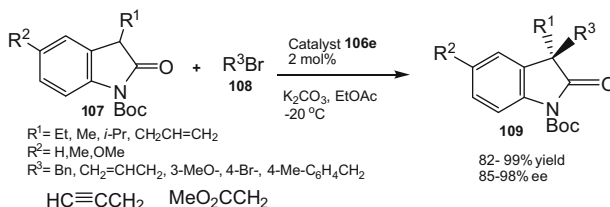
Scheme 30 Synthesis of phenylalanine derived anion-recognizing catalysts

photo sensitizers [113, 114], in oxidation of alcohols and in oxidative coupling of amines to imines or amides [115, 116]. 4,4'-bis(1,2,3-triazolium) salts served as precursors for bidentate ligands for Rh and are promising for potential application in asymmetric catalysis [24].

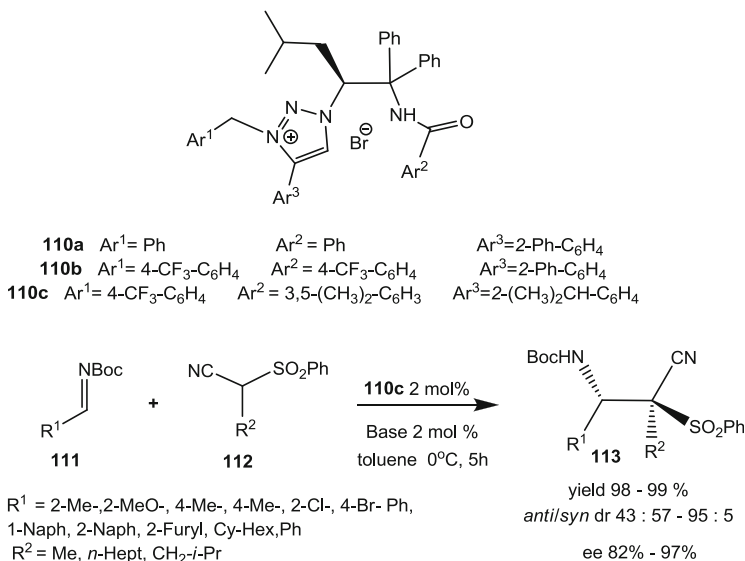
A very recent application of 1,2,3-triazolium salts as catalysts utilizes the ability of the 1,2,3-triazolium ring to engage in hydrogen bonding by its hydrogen atom at position 5 for anion recognition. The ability of 1,2,3-triazoles to form hydrogen bonds has long been exploited in peptide mimetics where the proton on carbon 5 serves as a hydrogen bond donor while the nitrogen at position 3 serves as hydrogen bond acceptor. The transformation of 1,2,3-triazoles to 1,2,3-triazolium salts by alkylation increases their hydrogen bonding ability due to an increased polarization of the C–H bond [59, 117, 118]. The ability of forming H–bonds can be exploited not only in catalysis but also in recognition of anions and in formation of supramolecular systems.

1,2,3-Triazolium-tagged organocatalysts **106** were synthesized starting from Boc protected phenylalanine, which was converted to 2-amino-1,1,3-triphenylpropane-1-ol hydrochloride **101** by Grignard reaction and deprotection. Diazo transfer provided the azidoalcohol **103** used for CuAAC and the resulting triazole **104** was transformed into the 1,2,3-triazolium salts **106** by OH-substitution and benzylation (Scheme 30).

The 1,2,3-triazolium salts **106** were found to be very efficient as catalysts (2% catalyst loading) for asymmetric carbon–carbon bond forming reactions between oxindoles **107** and alkyl bromides **108** in a wide scope providing oxindoles **109** with a quaternary carbon atom in excellent enantioselectivities (85–98%) and high yields (>82%) (Scheme 31). The reaction showed a wide scope. The catalytic activity and stereoselectivity was explained by formation of two H–bonds of the chiral 1,2,3-triazolium salt by the 5–H and the amide NH with the halide leaving group of the alkylating reagent as confirmed by X-ray diffraction analysis and NMR comparison between 1,2,3-triazolium salts with different counter anions.



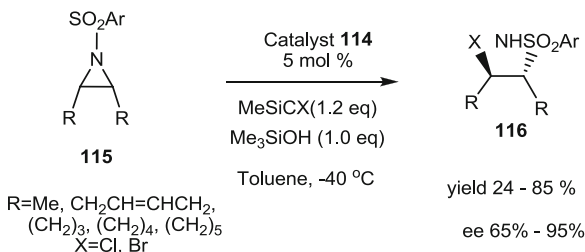
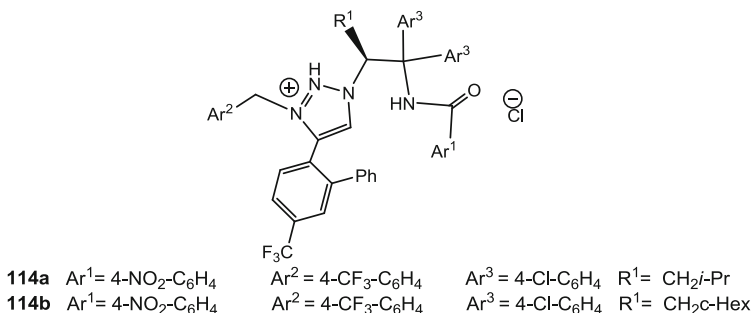
Scheme 31 Asymmetric alkylation of oxindoles catalysed by the 1,2,3-triazolium bromide **106e**



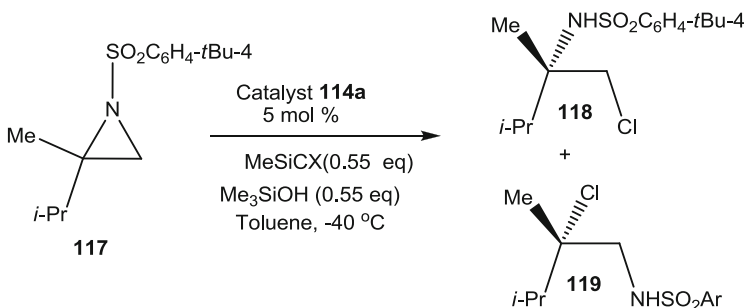
Scheme 32 Application of catalyst **110** in Mannich-type reaction of cyanosulphones

Similar chiral 1,2,3-triazolium salts such as **110** with anion recognition ability were proved to act as catalyst for asymmetric Mannich-type reaction of α -cyanosulphones with *N*-Boc imines (Scheme 32) [73]. Here, the hydrogen bonding occurred to a sulphonyl carbanion. The efficiency of the catalytic system was improved by choosing appropriate substituents, which were optimal in case of **110c** leading to excellent yields, anti/syn ratios up to > 95:5 and ee up to 97% of the products **113**.

Structurally similar 1,2,3-triazolium salts **114** and others were found to catalyse enantioselective ring opening of *meso*-aziridines **115** by halides using trimethylsilyl halides (chloride or bromide) as halide source. A hypervalent chlorosilicate (formed by the addition of the chloride anion from 1,2,3-triazolium salt to trimethylsilyl chloride) was proposed as reactive intermediate. The structure of the catalytic 1,2,3-triazolium salts **114** was optimized by providing high anion binding ability to the hypervalent silicate and thus improving the asymmetric induction reaching 95% ee (Scheme 33) [72].



Scheme 33 Catalytic asymmetric ring openings of *meso*-aziridines with halides catalysed by **114**



Scheme 34 Kinetic resolution of 2,2-disubstituted aziridines mediated by 1,2,3-triazolium ionic liquid **114a**

The same 1,2,3-triazolium salts **114** were also applied in kinetic resolution of racemic aziridines, e. g. **117** (Scheme 34) [72]. When the aziridines **117** were treated with Me₃SiCl (0.55 equiv) in the presence of **114a** (5 mol%) and Me₃SiOH (0.55 equiv) in toluene at -40 °C a regioisomeric mixture of the chlorinated products **118** and **119** arising from the stereo-invertive ring opening of the (*R*)-aziridine was isolated. The combined yield was 48% (131/132 = 80:20) with 90% enantioselectivity of the major β-chloroamine derivative **118**, while the (*S*)-**117** was recovered in 46% yield in enantiopure form [72].

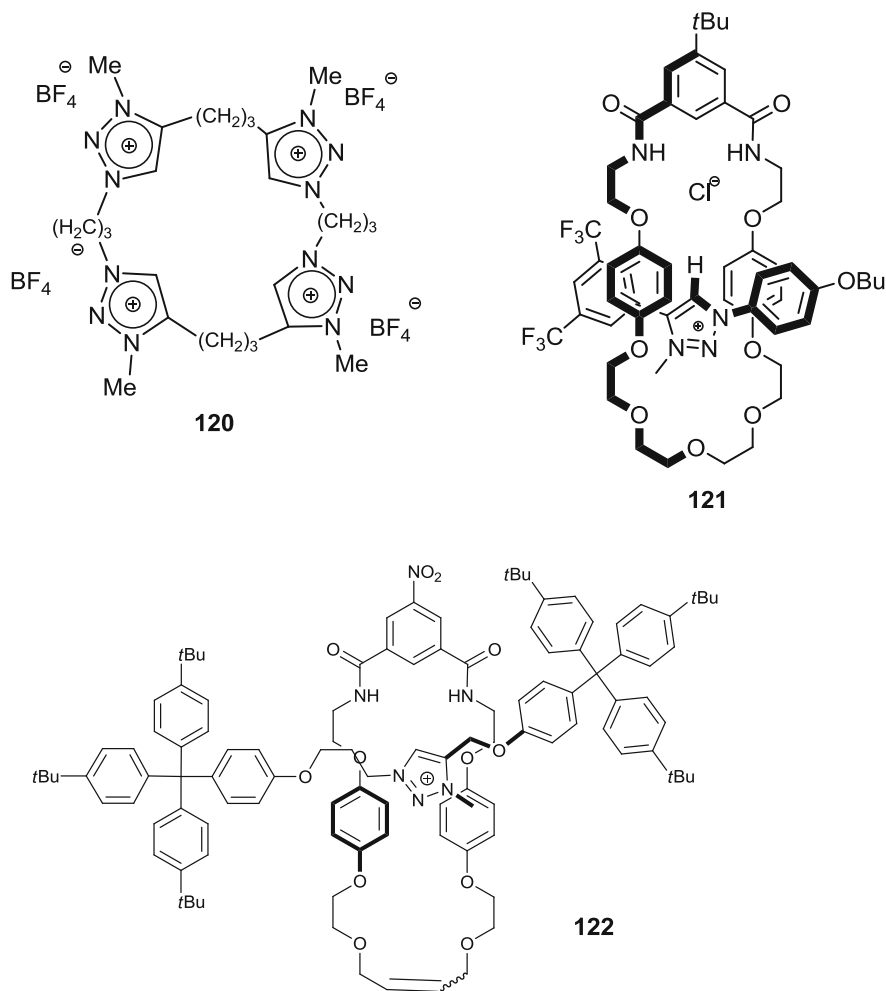


Fig. 3 1,2,3-Triazolium salts **120** and triazolium salt containing rotaxanes **121** and **122** with anion binding properties

5 Miscellaneous

1,2,3-Triazolium salts have entered the field of supramolecular chemistry and even of molecular machines. Here again, often the ability of forming H-bonds via the hydrogen atoms found at position 4 or 5 is involved. Thus, the cyclic tetra-1,2,3-triazolium salt **120** acted as a strong anion binder [64]. The pseudorotaxanes **121** and **122** with 1,2,3-triazolium-containing threads served as hosts for anions and were able to recognize halides (chloride or bromide) selectively [118].

An analogue of **122** with an iodo-substituent at the triazolium ring showed an unusual specific recognition for iodide [119] (Figs. 3 and 4).

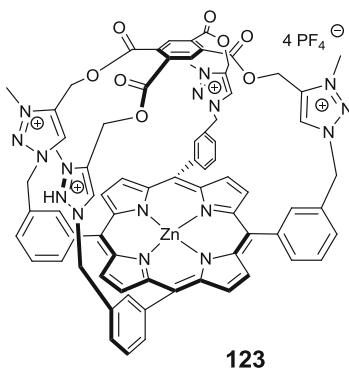


Fig. 4 1,2,3-triazolium-porphyrin cage **123** with selective sulphate anion recognition properties

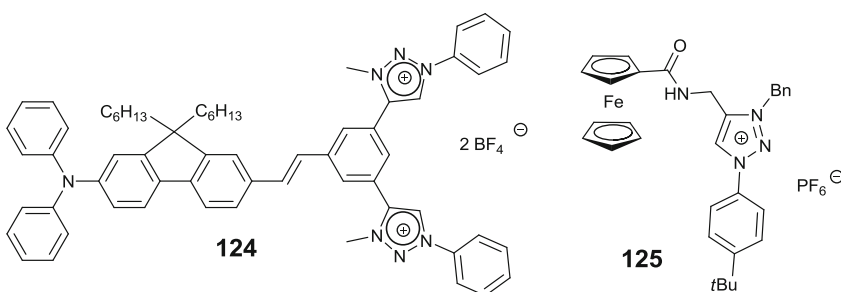


Fig. 5 1,2,3-Triazolium salts **124** and **125** with fluoride sensing properties

The 1,2,3-triazolium-porphyrin cage **123** exhibited a strong preference to include sulphate ions in the presence of halide ions [120].

The fluorene derivative **124** with two 1,2,3-triazolium units represents a highly selective fluoride sensor [121]. A marked electrochemical selectivity again for fluoride was found with a ferrocene-based anion receptor **125** containing a 1,2,3-triazolium donor group [122] (Fig. 5).

The 1,2,3-triazolium ring was also introduced into a nanomachine component **126** wherein it causes pH-sensitive two station shuttling by protonation of an amino group [123] (Fig. 6).

The 1,2,3-triazolium unit played a double role in the “lasso-based” molecular switch **127** by acting as a bulky gate for the cycle and a second molecular station [124] (Fig. 7).

The di-1,2,3-triazolium salt **128** was used as a component in a molecular “double-leg elevator” operating by the same principle [125] (Fig. 8).

Two molecules of the triazolium-containing chain compound **129** were involved in the construction of two-station [3]-rotaxane with an oligoethyleneglycol ether-containing rings [126]. Again, deprotonation/protonation of an amino group caused the movement of the molecular threads (Fig. 9).

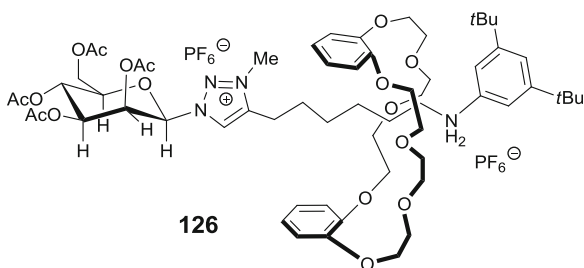


Fig. 6 1,2,3-triazolium salt containing nanomachine component

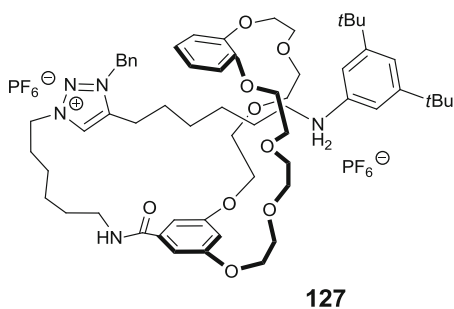


Fig. 7 Molecular switch **127** containing a 1,2,3-triazolium salt

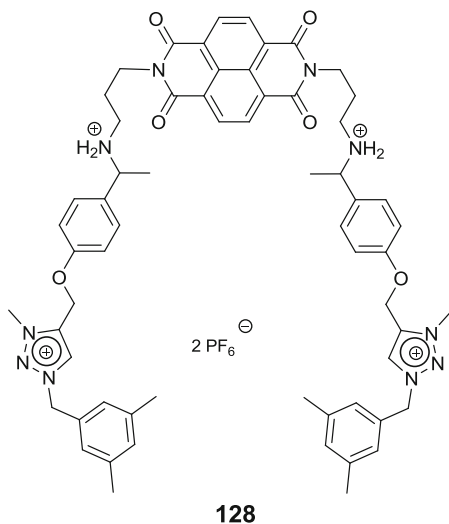


Fig. 8 1,2,3-Triazolium salt **128** as component for a molecular machine

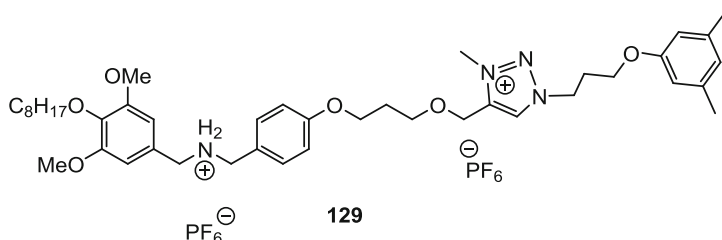


Fig. 9 1,2,3-triazolium salt **129** as a thread for a switchable two-station rotaxane

6 Summary

1,2,3-Triazolium salts have developed from being a common type of heterocycles to an impressive class of ILs. Their synthesis is straightforward including the CuAAC, *N*-alkylation and eventual salt metathesis in most cases. It also has a wide scope and thus allows to tune the properties of the 1,2,3-triazolium ILs as well as to functionalize them by one or more applicatory groups. The latter property is mainly exploited in catalysis so far. In addition to the use of the 1,2,3-triazolium moiety as a support for catalysts there is recent impressive application as precursors for unusual NHC ligands for metals providing catalytic properties better than conventional NHC. 1,2,3-Triazolium ILs also provides perspectives in other fields, such as in supramolecular chemistry and molecular switches or machines. The impact of 1,2,3-triazolium ILs would heavily increase if such materials will be produced in an industrial scale and become commercially available.

References

1. Zhou ZB, Matsumoto H, Tatsumi K (2005) Low-melting, low-viscous, hydrophobic ionic liquids: aliphatic quaternary ammonium salts with perfluoroalkyltrifluoroborates. *Chem Eur J* 11:7522
2. Sun J, Forsyth M, MacFarlane DR (1998) Room-temperature molten salts based on the quaternary ammonium ion. *J Phys Chem B* 102:88583
3. Tokuda H, Hayamizu K, Ishii K, Susan MABH, Watanabe M (2005) Physicochemical properties and structures of room temperature ionic liquids. 2. Variation of alkyl chain length in imidazolium cation. *J Phys Chem B* 109:61034
4. Zhou ZB, Matsumoto H, Tatsumi K (2004) Low-melting, low-viscous, hydrophobic ionic liquids: 1-alkyl(alkyl ether)-3-methylimidazolium perfluoroalkyltrifluoroborate. *Chem Eur J* 10:65815
5. Bonhote P, Dias AP, Papageorgiou N, Kalyanasundaram K, Gratzel M (1996) Hydrophobic, highly conductive ambient-temperature molten salts. *Inorg Chem* 35:11686
6. Saravanamurugan S, Fehrmann R, Riisager A (2012) Synthesis and characterization of ammonium-, pyridinium-, and pyrrolidinium-based sulfonamido functionalized ionic liquids. *Synthetic Commun* 42:33837

7. Fraser KJ, MacFarlane DR (2009) Phosphonium-based ionic liquids: an overview. *Aust J Chem* 62:3098
8. Khan SS, Hanelt S, Liebscher J (2009) Versatile synthesis of 1, 2, 3-triazolium-based ionic liquids. *Arkivoc* xii:1939
9. Hanelt S, Liebscher J (2008) A novel and versatile access to task-specific ionic liquids based on 1,2,3-triazolium salts. *Synlett* 7:1058
10. Drake G, Hawkins T, Tollison K, Hall L, Vij A, Sobaski S (2005) (1R)-4-amino-1,2,4-triazolium salts: New families of ionic liquids. *ACS Sym Ser* 902:259
11. Borowiecki P, Poterala M, Maurin J, Wielechowska M, Pleniewicz J (2012) Preparation and thermal stability of optically active 1,2,4-triazolium-based ionic liquids. *Arkivoc* 2012:262
12. Aupoix A, Vo-Thanh G (2009) Solvent-free synthesis of Alkylthiazolium-based ionic liquids and their use as catalysts in the intramolecular Stetter reaction. *Synlett* 12:1915
13. Hillesheim PC, Mahurin SM, Fulvio PF, Yeary JS, Oyola Y, Jiang DE, Dai S (2012) Synthesis and characterization of thiazolium-based room temperature ionic liquids for gas separations. *Ind Eng Chem Res* 51:11530
14. Zhang QH, Liu SM, Li ZP, Li J, Chen ZJ, Wang RF, Lu LJ, Deng YQ (2009) Novel cyclic sulfonium-based ionic liquids: synthesis, characterization, and physicochemical properties. *Chem Eur J* 15:765
15. Chiappe C, Sanzone A, Mendola D, Castiglione F, Famulari A, Raos G, Mele A (2013) Pyrazolium- versus imidazolium-based ionic liquids: structure, dynamics and physicochemical properties. *J Phys Chem B* 117:668
16. Chai M, Jin YD, Fang SH, Yang L, Hirano S, Tachibana K (2012) Low-viscosity ether-functionalized pyrazolium ionic liquids as new electrolytes for lithium battery. *J Power Sources* 216:323
17. Rogers RD, Seddon KR, American Chemical Society, Division of Industrial and Engineering Chemistry, American Chemical Society. Meeting (2002) Ionic liquids: industrial applications for green chemistry. American Chemical Society, Washington, D.C., xiv 474 p
18. Wasserscheid P, Welton T (2003) Ionic liquids in synthesis. Wiley-VCH, Weinheim, xvi p
19. Dupont J, de Souza RF, Suarez PAZ (2002) Ionic liquid (molten salt) phase organometallic catalysis. *Chem Rev* 102:3667
20. Welton T (1999) Room-temperature ionic liquids. Solvents for synthesis and catalysis. *Chem Rev* 99:2071
21. Sowmiah S, Srinivasadesikan V, Tseng MC, Chu YH (2009) On the chemical stabilities of ionic liquids. *Molecules* 14:3780
22. Plechkova NV, Seddon KR (2008) Applications of ionic liquids in the chemical industry. *Chem Soc Rev* 37:123
23. Yacob Z, Liebscher J (2011) 1,2,3-Triazolium salts as a versatile new class of ionic liquids. In: Handy TS (ed) Ionic liquids – classes and properties, InTech: 2011, vol Part 1, DOI:[10.5772/24349](https://doi.org/10.5772/24349)
24. Aizpurua JM, Fratila RM, Monasterio Z, Pérez-Esnaola N, Andreieff E, Irastorza A, Sagartzazu-Aizpurua M (2014) Triazolium cations: from the “click” pool to multipurpose applications. *New J Chem* 38:474
25. Hein JE, Fokin VV (2010) Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides. *Chem Soc Rev* 39:1302
26. Gompper R (1957) Untersuchungen in Der Azolreihe.5. Umsetzungen Der Oxazolone-(2) Mit Metallorganischen Verbindungen. *Chem Ber* 90:374
27. Kolb HC, Finn MG, Sharpless KB (2001) Click chemistry: Diverse chemical function from a few good reactions. *Angew Chem Int Ed* 40:2004
28. Tornøe CW, Christensen C, Meldal M (2002) Peptidotriazoles on solid phase: [1,2,3]-triazoles by regioselective copper(I)-catalyzed 1,3-dipolar cycloadditions of terminal alkynes to azides. *J Org Chem* 67:3057
29. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB (2002) A stepwise Huisgen cycloaddition process: Copper(I)-catalyzed regioselective “ligation” of azides and terminal alkynes. *Angew Chem Int Ed* 41:2596

30. Rodionov VO, Presolski SI, Diaz DD, Fokin VV, Finn MG (2007) Ligand-accelerated Cu-catalyzed azide-alkyne cycloaddition: a mechanistic report. *J Am Chem Soc* 129:12705
31. Rodionov VO, Presolski SI, Gardinier S, Lim YH, Finn MG (2007) Benzimidazole and related ligands for Cu-catalyzed azide-alkyne cycloaddition. *J Am Chem Soc* 129:12696
32. Liu MN, Reiser O (2011) A Copper(I) isonitrile complex as a heterogeneous catalyst for azide-alkyne cycloaddition in water. *Org Lett* 13:1102
33. Orgueira HA, Fokas D, Isome Y, Chan PCM, Baldino CM (2005) Regioselective synthesis of [1,2,3]-triazoles catalyzed by Cu(I) generated in situ from Cu(0) nanosize activated powder and amine hydrochloride salts. *Tetrahedron Lett* 46:2911
34. Pachon LD, van Maarseveen JH, Rothenberg G (2005) Click chemistry: Copper clusters catalyse the cycloaddition of azides with terminal alkynes. *Adv Synth Catal* 347:811
35. Baig RBN, Varma RS (2013) Copper on chitosan: a recyclable heterogeneous catalyst for azide-alkyne cycloaddition reactions in water. *Green Chem* 15:1839
36. Wittig G, Krebs A (1961) Zur Existenz Niedergliedriger Cycloalkine .1. *Chem Ber-Recl* 94:3260
37. Baskin JM, Prescher JA, Laughlin ST, Agard NJ, Chang PV, Miller IA, Lo A, Codelli JA, Bertozzi CR (2007) Copper-free click chemistry for dynamic in vivo imaging. *Proc Natl Acad Sci U S A* 104:16793
38. Debets MF, van Berkel SS, Schoffelen S, Rutjes FPJT, van Hest JCM, van Delft FL (2010) Aza-dibenzocyclooctynes for fast and efficient enzyme PEGylation via copper-free (3+2) cycloaddition. *Chem Commun* 46:97
39. Bernardin A, Cazet A, Guyon L, Delannoy P, Vinet F, Bonnaffe D, Texier I (2010) Copper-free click chemistry for highly luminescent quantum dot conjugates: application to in vivo metabolic imaging. *Bioconjug Chem* 21:583
40. Kwok SW, Fotsing JR, Fraser RJ, Rodionov VO, Fokin VV (2010) Transition-metal-free catalytic synthesis of 1,5-diaryl-1,2,3-triazoles. *Org Lett* 12:4217
41. Yan JC, Wang L (2010) Synthesis of 1,4-disubstituted 1,2,3-triazoles by use of copper(I) and amino acids ionic liquid catalytic system. *Synthesis* 3:447
42. Fletcher JT, Keeney ME, Walz SE (2010) 1-Allyl- and 1-benzyl-3-methyl-1,2,3-triazolium salts via tandem click transformations. *Synthesis* 19:3339
43. Zhang L, Chen X, Xue P, Sun HH, Williams ID, Sharpless KB, Fokin VV, Jia G (2005) Ruthenium-catalyzed cycloaddition of alkynes and organic azides. *J Am Chem Soc* 127:15998
44. Johansson JR, Lincoln P, Norden B, Kann N (2011) Sequential one-pot ruthenium-catalyzed azide-alkyne cycloaddition from primary alkyl halides and sodium azide. *J Org Chem* 76:2355
45. Chuprakov S, Chernyak N, Dudnik AS, Gevorgyan V (2007) Direct Pd-catalyzed arylation of 1,2,3-triazoles. *Org Lett* 9:2333
46. Coats SJ, Link JS, Gauthier D, Hlasta DJ (2005) Trimethylsilyl-directed 1,3-dipolar cycloaddition reactions in the solid-phase synthesis of 1,2,3-triazoles. *Org Lett* 7:1469
47. Kloss F, Kohn U, Jahn BO, Hager MD, Gorls H, Schubert US (2011) Metal-free 1,5-regioselective azide-alkyne [3+2]-cycloaddition. *Chem Asian J* 6:2816
48. Koguchi S, Izawa K (2012) A new method for the synthesis of 1,5-disubstituted 1,2,3-triazoles via triazolium salt intermediates. *Synthesis* 44:3603
49. Begtrup M (1971) Reactions between azolium salts and nucleophilic reagents.2. Bromo-1,2,3-triazolium salts and sodium hydroxide. *Acta Chem Scand* 25:249
50. Drake G, Hawkins T, Brand A, Hall L, McKay M, Vij A, Ismail I (2003) Energetic, low-melting salts of simple heterocycles. *Propell Explos Pyrot* 28:174
51. Khan SS, Shah J, Liebscher J (2010) Synthesis of new ionic-liquid-tagged organocatalysts and their application in stereoselective direct aldol reactions. *Tetrahedron* 66:5082
52. Jeong Y, Ryu JS (2010) Synthesis of 1,3-dialkyl-1,2,3-triazolium ionic liquids and their applications to the Baylis-Hillman reaction. *J Org Chem* 75:4183

53. Begtrup M, Larsen P (1990) Alkylation, acylation and silylation of azoles. *Acta Chem Scand* 44:1050
54. Jeong Y, Kim DY, Choi Y, Ryu JS (2011) Intramolecular hydroalkoxylation in Bronsted acidic ionic liquids and its application to the synthesis of (+/-)-centrolobine. *Org Biomol Chem* 9:374
55. Yoshida Y, Takizawa S, Sasai H (2012) Design and synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids. *Tetrahedron Asymmetry* 23:843
56. Yoshida Y, Takizawa S, Sasai H (2011) Synthesis of spiro bis(1,2,3-triazolium) salts as chiral ionic liquids. *Tetrahedron Lett* 52:6877
57. Aizpurua JM, Sagartzazu-Aizpurua M, Azcune I, Miranda JI, Monasterio Z, Garcia-Lecina E, Fratila RM (2011) 'Click' synthesis of nonsymmetrical 4,4'-Bis(1,2,3-triazolium) salts. *Synthesis* 17:2737
58. Khan SS, Liebscher J (2010) Synthesis of new dicationic azolium salts and their application as NHC precursors in Suzuki–Miyaura coupling. *Synthesis* 15:2609
59. Schulze B, Friebe C, Hager MD, Gunther W, Kohn U, Jahn BO, Gorls H, Schubert US (2010) Anion complexation by triazolium "Ligands": mono- and bis-tridentate complexes of sulfate. *Org Lett* 12:2710
60. Dimitrov-Raychev P, Beghdadi S, Serghei A, Drockenmuller E (2013) Main-chain 1,2,3-triazolium-based poly(ionic liquid)s issued from AB plus AB click chemistry polyaddition. *J Polym Sci Polym Chem* 51:34
61. Mathew P, Neels A, Albrecht M (2008) 1,2,3-triazolyliidenes as versatile abnormal carbene ligands for late transition metals. *J Am Chem Soc* 130:13534
62. Yacob Z, Shah J, Leistner J, Liebscher J (2008) (S)-pyrrolidin-2-ylmethyl-1,2,3-triazolium salts – Ionic liquid supported organocatalysts for enantioselective Michael additions to beta-nitrostyrenes. *Synlett* 15:2342
63. Allen JJ, Schneider Y, Kail BW, Luebke DR, Nulwala H, Damodaran K (2013) Nuclear spin relaxation and molecular interactions of a novel triazolium-based ionic liquid. *J Phys Chem B* 117:3877
64. White NG, Carvalho S, Felix V, Beer PD (2012) Anion binding in aqueous media by a tetra-triazolium macrocycle. *Org Biomol Chem* 10:6951
65. Tseng MC, Cheng HT, Shen MJ, Chu YH (2011) Bicyclic 1,2,3-triazolium ionic liquids: synthesis, characterization, and application to Rutaecarpine synthesis. *Org Lett* 13:4434
66. Shah J, Khan SS, Blumenthal H, Liebscher J (2009) 1,2,3-Triazolium-tagged prolines and their application in asymmetric Aldol and Michael reactions. *Synthesis* 23:3975
67. Khan SS, Shah J, Liebscher J (2011) Ionic-liquid tagged prolines as recyclable organocatalysts for enantioselective α -aminoxylations of carbonyl compounds. *Tetrahedron* 67:1812
68. Maltsev OV, Kucherenko AS, Chimishkyan AL, Zlotin SG (2010) α,α -Diarylprolinol-derived chiral ionic liquids: recoverable organocatalysts for the domino reaction between α,β -enals and N-protected hydroxylamines. *Tetrahedron Asymmetry* 21:2659
69. Siyutkin DE, Kucherenko AS, Struchkova MI, Zlotin SG (2008) A novel (S)-proline-modified task-specific chiral ionic liquid – an amphiphilic recoverable catalyst for direct asymmetric aldol reactions in water. *Tetrahedron Lett* 49:1212
70. Yacob Z, Liebscher J (2012) Synthesis and application of Azolium ionic liquid tagged TADDOL catalysts. *Arkivoc* 2012:312
71. Ohmatsu K, Kiyokawa M, Ooi T (2011) Chiral 1,2,3-triazoliums as new cationic organic catalysts with anion-recognition ability: application to asymmetric alkylation of oxindoles. *J Am Chem Soc* 133:1307
72. Ohmatsu K, Hamajima Y, Ooi T (2012) Catalytic asymmetric ring openings of meso and terminal aziridines with halides mediated by chiral 1,2,3-triazolium silicates. *J Am Chem Soc* 134:8794

73. Ohmatsu K, Goto A, Ooi T (2012) Catalytic asymmetric Mannich-type reactions of α -cyano α -sulfonyl carbanions. *Chem Commun* 48:7913
74. Sanghi S, Willett E, Versek C, Tuominen M, Coughlin EB (2012) Physicochemical properties of 1,2,3-triazolium ionic liquids. *RSC Adv* 2:848
75. Bini R, Bortolini O, Chiappe C, Pieraccini D, Siciliano T (2007) Development of cation/anion "interaction" scales for ionic liquids through ESI-MS measurements. *J Phys Chem B* 111:598
76. Forsyth SA, MacFarlane DR (2003) 1-Alkyl-3-methylbenzotriazolium salts: ionic solvents and electrolytes. *J Mater Chem* 13:2451
77. Reiter J, Jeremias S, Paillard E, Winter M, Passerini S (2013) Fluorosulfonyl-(trifluoromethanesulfonyl)imide ionic liquids with enhanced asymmetry. *Phys Chem Chem Phys* 15:2565
78. Dupont J, Spencer J (2004) On the noninnocent nature of 1,3-dialkylimidazolium ionic liquids. *Angew Chem Int Ed Engl* 43:5296
79. Guisado-Barrios G, Bouffard J, Donnadiou B, Bertrand G (2010) Crystalline 1H-1,2,3-triazol-5-ylidenes: new stable mesoionic carbenes (MICs). *Angew Chem Int Ed* 49:4759
80. Kan HC, Tseng MC, Chu YH (2007) Bicyclic imidazolium-based ionic liquids: synthesis and characterization. *Tetrahedron* 63:1644
81. Crowley JD, Lee AL, Kilpin KJ (2011) 1,3,4-Trisubstituted-1,2,3-triazol-5-ylidene 'click' carbene ligands: synthesis, catalysis and self-assembly. *Aust J Chem* 64:1118
82. Donnelly KF, Petronilho A, Albrecht M (2013) Application of 1,2,3-triazolylidenes as versatile NHC-type ligands. *Chem Commun* 49:1145
83. Rosa JN, Afonso CAM, Santos AG (2001) Ionic liquids as a recyclable reaction medium for the Baylis-Hillman reaction. *Tetrahedron* 57:4189
84. Miao WS, Chan TH (2006) Ionic-liquid-supported organocatalyst: Efficient and recyclable ionic-liquid-anchored proline for asymmetric aldol reaction. *Adv Synth Catal* 348:1711
85. Lombardo M, Pasi F, Easwar S, Trombini C (2007) An improved protocol for the direct asymmetric aldol reaction in ionic liquids, catalysed by onium ion-tagged prolines. *Adv Synth Catal* 349:2061
86. Davis JH (2004) Task-specific ionic liquids. *Chem Lett* 33:1072
87. Yang SD, Shi Y, Sun ZH, Zhao YB, Liang YM (2006) Asymmetric borane reduction of prochiral ketones using imidazolium-tagged sulfonamide catalyst. *Tetrahedron Asymmetry* 17:1895
88. Zhou L, Wang L (2007) Chiral ionic liquid containing L-proline unit as a highly efficient and recyclable asymmetric organocatalyst for aldol reaction. *Chem Lett* 36:628
89. Khan SS, Shah J, Liebscher J (2010) Synthesis of new ionic-liquid-tagged organocatalysts and their application in stereoselective direct aldol reactions. *Tetrahedron* 66:9468
90. Yan ZY, Niu YN, Wei HL, Wu LY, Zhao YB, Liang YM (2006) Combining proline and 'click chemistry': a class of versatile organocatalysts for the highly diastereo- and enantioselective Michael addition in water. *Tetrahedron Asymmetry* 17:3288
91. Hagiwara H, Okabe T, Hakoda K, Hoshi T, Ono H, Kamat VP, Suzuki T, Ando M (2001) Catalytic enamine reaction: an expedient 1,4-conjugate addition of naked aldehydes to vinylketones and its application to synthesis of cyclohexenone from *Stevia purpurea*. *Tetrahedron Lett* 42:2705
92. Zekarias Y (2010) 1,2,3-triazolium ionic liquid tagged catalysts in asymmetric organocatalysis monograph. Humboldt University of Berlin, Berlin
93. Gajewski M, Seaver B, Esslinger CS (2007) Design, synthesis, and biological activity of novel triazole amino acids used to probe binding interactions between ligand and neutral amino acid transport protein SN1. *Bioorg Med Chem Lett* 17:4163
94. Seebach D, Beck AK, Heckel A (2001) TADDOLs, their derivatives, and TADDOL analogues: versatile chiral auxiliaries. *Angew Chem Int Ed* 40:92
95. Huang Y, Rawal VH (2002) Hydrogen-bond-promoted hetero-Diels-Alder reactions of unactivated ketones. *J Am Chem Soc* 124:9662

96. Saravanakumar R, Ramkumar V, Sankararaman S (2013) Synthesis and structural characterization of *cis* isomer of 1,2,3-triazol-5-ylidene based palladium complexes. *J Organomet Chem* 736:36
97. Guisado-Barrios G, Bouffard J, Donnadiou B, Bertrand G (2011) Bis(1,2,3-triazol-5-ylidenes) (i-bitz) as Stable 1,4-Bidentate ligands based on Mesoionic Carbenes (MICs). *Organometallics* 30:6017
98. Aizpurua JM, Sagartzazu-Aizpurua M, Monasterio Z, Azcune I, Mendicute C, Miranda JJ, Garcia-Lecina E, Altube A, Fratila RM (2012) Introducing axial chirality into mesoionic 4,4'-Bis(1,2,3-triazole) Dicarbenes. *Org Lett* 14:1866
99. Nakamura T, Ogata K, Fukuzawa S (2010) Synthesis of Dichlorobis(1,4-dimesityl-1H-1,2,3-triazol-5-ylidene)palladium [PdCl₂(TMes)₂] and its application to Suzuki-Miyaura coupling reaction. *Chem Lett* 39:920
100. Terashima T, Inomata S, Ogata K, Fukuzawa S (2012) Synthetic, structural, and catalytic studies of well-defined allyl 1,2,3-triazol-5-ylidene (tzNHC) palladium complexes. *Eur J Inorg Chem* 9:1387
101. Canseco-Gonzalez D, Gniewek A, Szulmanowicz M, Muller-Bunz H, Trzeciak AM, Albrecht M (2012) PEPPSI-type palladium complexes containing basic 1,2,3-triazolylidene ligands and their role in Suzuki-Miyaura catalysis. *Chem Eur J* 18:6055
102. Inomata S, Hiroki H, Terashima T, Ogata K, Fukuzawa S (2011) 1,2,3-Triazol-5-ylidene-palladium complex catalyzed Mizoroki-Heck and Sonogashira coupling reactions. *Tetrahedron* 67:7263
103. Keske EC, Zenkina OV, Wang RY, Crudden CM (2012) Synthesis and structure of palladium 1,2,3-triazol-5-ylidene mesoionic carbene PEPPSI complexes and their catalytic applications in the Mizoroki-Heck reaction. *Organometallics* 31:6215
104. Nakamura T, Terashima T, Ogata K, Fukuzawa S (2011) Copper(I) 1,2,3-Triazol-5-ylidene complexes as efficient catalysts for click reactions of azides with alkynes. *Org Lett* 13:620
105. Hohloch S, Sarkar B, Nauton L, Cisnetti F, Gautier A (2013) Are Cu(I)-mesoionic NHC carbenes associated with nitrogen additives the best Cu-carbene catalysts for the azide-alkyne click reaction in solution? A case study. *Tetrahedron Lett* 54:1808
106. Hohloch S, Su CY, Sarkar B (2011) Copper(I) complexes of normal and abnormal carbenes and their use as catalysts for the Huisgen [3+2] cycloaddition between azides and alkynes. *Eur J Inorg Chem* 20:3067
107. Klein JEMN, Holzwarth MS, Hohloch S, Sarkar B, Plietker B (2013) Redox-active triazolium-derived ligands in nucleophilic Fe-catalysis – reactivity profile and development of a regioselective O-allylation. *Eur J Org Chem* 2013:6310
108. Nomura R, Tsuchiya Y, Ishikawa H, Okamoto S (2013) Grignard allylic substitution reaction catalyzed by 1,2,3-triazol-5-ylidene magnesium complexes. *Tetrahedron Lett* 54:1360
109. Bouffard J, Keitz BK, Tonner R, Guisado-Barrios G, Frenking G, Grubbs RH, Bertrand G (2011) Synthesis of highly stable 1,3-diaryl-1H-1,2,3-triazol-5-ylidenes and their applications in ruthenium-catalyzed olefin metathesis. *Organometallics* 30:2617
110. Petronilho A, Rahman M, Woods JA, Al-Sayyed H, Muller-Bunz H, MacElroy JMD, Bernhard S, Albrecht M (2012) Photolytic water oxidation catalyzed by a molecular carbene iridium complex. *Dalton T* 41:13074
111. Lalrempuia R, McDaniel ND, Muller-Bunz H, Bernhard S, Albrecht M (2010) Water oxidation catalyzed by strong carbene-type donor-ligand complexes of iridium. *Angew Chem Int Ed* 49:9765
112. Bernet L, Lalrempuia R, Ghattas W, Mueller-Bunz H, Vigara L, Llobet A, Albrecht M (2011) Tunable single-site ruthenium catalysts for efficient water oxidation. *Chem Commun* 47:8058
113. Schulze B, Escudero D, Friebe C, Siebert R, Gorls H, Kohn U, Altuntas E, Baumgaertel A, Hager MD, Winter A, Dietzek B, Popp J, Gonzalez L, Schubert US (2011) A heteroleptic bis (tridentate) ruthenium(II) complex of a click-derived abnormal carbene pincer ligand with potential for photosensitizer application. *Chem Eur J* 17:5494

114. Leigh V, Ghattas W, Lalrempuia R, Muller-Bunz H, Pryce MT, Albrecht M (2013) Synthesis, photo-, and electrochemistry of ruthenium bis(bipyridine) complexes comprising a N-heterocyclic carbene ligand. *Inorg Chem* 52:5395
115. Prades A, Peris E, Albrecht M (2011) Oxidations and oxidative couplings catalyzed by triazolyldiene ruthenium complexes. *Organometallics* 30:1162
116. Canseco-Gonzalez D, Albrecht M (2013) Wingtip substituents tailor the catalytic activity of ruthenium triazolyldiene complexes in base-free alcohol oxidation. *Dalton T* 42:7424
117. Kumar A, Pandey PS (2008) Anion recognition by 1,2,3-triazolium receptors: Application of click chemistry in anion recognition. *Org Lett* 10:165
118. Mullen KM, Mercurio J, Serpell CJ, Beer PD (2009) Exploiting the 1,2,3-Triazolium Motif in anion-templated formation of a bromide-selective rotaxane host assembly. *Angew Chem Int Ed* 48:4781
119. Kilah NL, Wise MD, Serpell CJ, Thompson AL, White NG, Christensen KE, Beer PD (2010) Enhancement of anion recognition exhibited by a halogen-bonding rotaxane host system. *J Am Chem Soc* 132:11893
120. Gilday LC, White NG, Beer PD (2012) Triazole- and triazolium-containing porphyrin-cages for optical anion sensing. *Dalton T* 41:7092
121. Sui BL, Kim B, Zhang YW, Frazer A, Belfield KD (2013) Highly selective fluorescence turn-on sensor for fluoride detection. *ACS Appl Mater Inter* 5:2920
122. Cao QY, Pradhan T, Lee MH, No K, Kim JS (2012) Ferrocene-based anion receptor bearing amide and triazolium donor groups. *Analyst* 137:4454
123. Coutrot F, Busseron E (2008) A new glycorotaxane molecular machine based on an anilinium and a triazolium station. *Chem Eur J* 14:4784
124. Clavel C, Romuald C, Brabet E, Coutrot F (2013) A pH-sensitive lasso-based rotaxane molecular switch. *Chem Eur J* 19:2982
125. Zhang ZJ, Han M, Zhang HY, Liu Y (2013) A double-leg donor-acceptor molecular elevator: new insight into controlling the distance of two platforms. *Org Lett* 15:1698
126. Jiang Y, Guo JB, Chen CF (2010) A New [3]Rotaxane molecular machine based on a dibenzylammonium ion and a triazolium station. *Org Lett* 12:4248

Top Heterocycl Chem (2015) 40: 211–268

DOI: 10.1007/7081_2014_120

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Published online: 20 July 2014

Mesoionic 1,2,3-Triazoles and 1,2,3-Triazole Carbenes

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Abstract Routine access to 1,2,3-triazoles through the copper-catalyzed azide-alkyne “click” cycloaddition reaction has promoted the rapid development of 1,2,3-triazolylidenes as ligands for transition metals. The organometallic complexes containing this kind of *N*-heterocyclic carbene ligands (NHCs) have shown to possess unique structural characteristics, including a relatively high covalent contribution to the metal–NHC bond, a strong donor ability, and a mesoionic character. Complexes of mesoionic triazolylidene carbenes (MICs) are readily available, among other methods, by metallation of N3-substituted 1,2,3-triazolium salts, usually followed by transmetallation reactions. A diverse array of monodentate, polydentate, and bridged ligands containing the 1,2,3-triazolylidene motif has been described, and the structures of complexes containing them have been characterized in detail. Promising applications in organometallic catalysis involving C–C and C–X bond formation and redox reactions have emerged in recent years for 1,2,3-triazolylidene metal complexes, and, owing to the modular and multiple functionalization possibilities around the 1,2,3-triazole scaffold, novel applications are expected in upcoming years.

Keywords 1,2,3-Triazolium salts · 1,2,3-Triazolylidenes · Carbenes · Homogeneous catalysis · Mesoionic compounds · Metallation · Transition metal complexes

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Abbreviations

Ac	Acetyl
adam	Adamantyl
Ag	Silver
Ar	Aryl
Au	Gold
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
Bpy	2,2'-Bipyridyl
Bu	Butyl
Bz	Benzoyl
CAN	Ceric ammonium nitrate
cat	Catalyst
cod	Cyclooctadiene
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
Cu	Copper
CuAAC	Copper-accelerated azide-alkyne cycloaddition
CV	Cyclic voltammetry
Cym	Cymene
d	Day(s)
DBU	1,8-Diazabicyclo [5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	<i>N,N</i> -Diisopropylethylamine

Dipp	2,6-Diisopropylphenyl
DMAP	4-(Dimethylamino)pyridine
DMB	3,4-Dimethoxybenzyl
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Dtm	Di(4-tolyl)methane
EDA	Ethyl diazoacetate
<i>ee</i>	Enantiomer excess
equiv	Equivalent(s)
Et	Ethyl
eV	Electron volt
GII	Grubbs' second-generation catalyst
h	Hour(s)
HMPA	Hexamethylphosphoric triamide
HOMO	Highest occupied molecular orbital
<i>i</i> Pr	Isopropyl
Ir	Iridium
KHMDS	Potassium hexamethyldisilazane, potassium bis(trimethylsilyl)amide
LUMO	Lowest unoccupied molecular orbital
M	Metal(s)
m.p.	Melting point
Me	Methyl
Mes	Mesityl, 2,4,6-trimethylphenyl
MIC	Mesoionic carbenes
min	Minute(s)
MLCT	Metal-to-ligand charge transfer
mol	Mole(s)
Ms	Methanesulfonyl (mesyl)
MS	Mass spectrometry
mV	Millivolt
Na Asc	Sodium ascorbate
NHC	<i>N</i> -heterocyclic carbene
Nu	Nucleophile
PA ₁	Proton affinity
Pd	Palladium
Ph	Phenyl
Pr	Propyl
py	Pyridine
RCM	Ring-closing metathesis
Re	Rhenium
Rh	Rhodium
ROMP	Ring-opening metathesis polymerization
rt	Room temperature

Ru	Ruthenium
s	Second(s)
<i>t</i> Bu	<i>tert</i> -Butyl
Tf	Trifluoromethanesulfonyl (triflyl)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tipp	2,4,6-Triisopropylphenyl
tmeda	<i>N,N,N',N'</i> -tetramethylenediamine
TMS	trimethylsilyl
TMSD	(Trimethylsilyl)-diazomethane
Tol	4-Methylphenyl
TON	Turnover number
Tpy	2,2',6',2''-Terpyridine

1 Introduction

N-Heterocyclic carbenes (NHCs) comprise a family of heterocyclic molecules containing a neutral divalent carbon with two unshared valence electrons stabilized by one or several nitrogen atoms in the ring. Unquestionably, the most popular NHCs are the 1,3-imidazole-based carbenes, which have been extensively crafted to form a wide variety of transition metal complexes, since their discovery by Arduengo two decades ago [1].

1,2,3-Triazoles can also form several kinds of triazolylidene structures including triazol-5-ylidenes **I** and **II** and triazol-4,5-diylidenes **III** (Fig. 1). The term “mesoionic” is assigned to carbenes that require additional charges in their resonance forms [2–6]. For example, neutral carbenes **I** can only be represented by Lewis structures containing positive and negative charges, whereas carbenes **II**, derived from 2*H*-1,2,3-triazoles, possess an uncharged Lewis structure and are not mesoionic. Analogously, anionic dicarbenes **III** can be represented without a positive charge. This review covers the synthesis, structural characteristic, and chemical applications of fully mesoionic and related carbenes comprising the 1,2,3-triazolylidene motif.

Triazolylienes, specially the mesoionic ones, are excellent ligands for transition metal ion coordination to form complexes. Such MIC complexes can be classified according to the coordination ability of the carbene ligand, the number of triazole units included in the ligand, and the chelating or open character of the coordination bonds formed with the metal. Combining these criteria, we have defined five main families of monodentate, polydentate, and bridged triazolylidene complexes (Fig. 2). Herein, we examine the preparation of triazolylidene complexes of types (A–J), focusing on the synthesis of the mesoionic ligands, their incorporation into transition metal complexes, and their use in organometallic catalysis.

Despite its recent creation, the chemistry of triazolylidene complexes is currently one of the most promising and fastest developing areas in *N*-heterocyclic

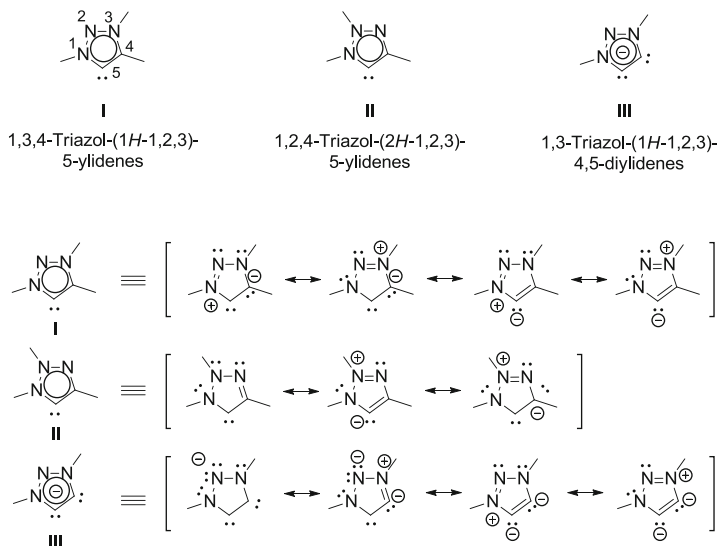


Fig. 1 *Top*: *N*-heterocyclic carbenes comprising the 1,2,3-triazole motif. *Bottom*: representative Lewis structures of mesoionic (**I**) and normal (**II**, **III**) 1,2,3-triazolyldiene carbenes

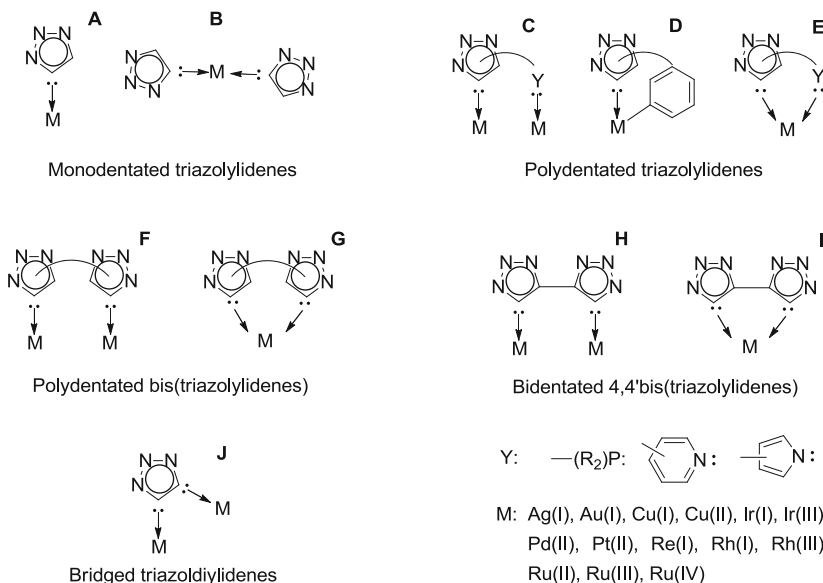
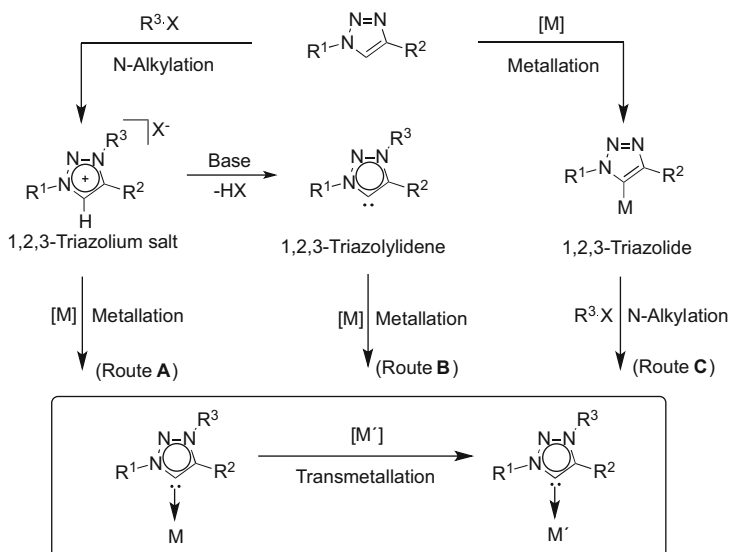


Fig. 2 Main molecular architectures of metal carbene complexes containing 1,2,3-triazolyldiene ligands covered in this review

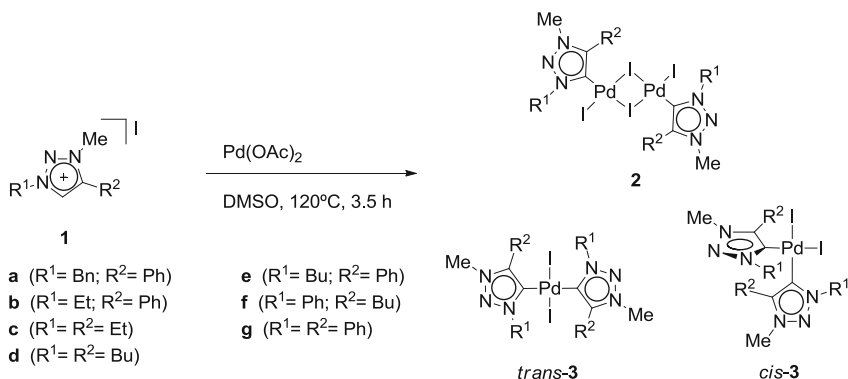


Scheme 1 Synthetic approaches to 1,2,3-triazolylidene complexes

carbenes. The topic has been surveyed by Albrecht in an excellent review covering aspects related to the preparation, donor properties, and catalytic activity of 1,2,3-triazolylidenes [7]. Crabtree has also partially reviewed the subject [8].

2 Synthetic Routes to Metal Triazolylidene Complexes

Transformation of 1,4-disubstituted 1,2,3-triazoles into 1,2,3-triazolylidene metal complexes can be achieved formally following the synthetic routes depicted in Scheme 1. 1,2,3-Triazoles are regioselectively *N*-alkylated at position N3 upon treatment with strong alkylating agents such as methyl iodide, alkyl triflates, or Meerwein salts ($R_3\text{OBF}_4$) to afford 1,3,4-trisubstituted triazolium salts. The preparation and chemical properties of such compounds are comprehensively covered in this book [98]. Triazolium salts can be directly metallated to triazolylidene complexes employing transition metal salts carrying basic anions (route A). Alternatively, they can be deprotonated to free triazole carbenes with strong bases and further metallated to the complexes in two separate steps (route B). The transformation sequence can be inverted metallating first the C5 position of the parent triazoles and then *N*-alkylating the resulting triazolide anions to the carbene complexes (route C). Finally, the range of accessible triazolylidene complexes can be considerably expanded by transmetalation of appropriate metal carbenes (typically silver carbenes) with exchange complexes of other metals.



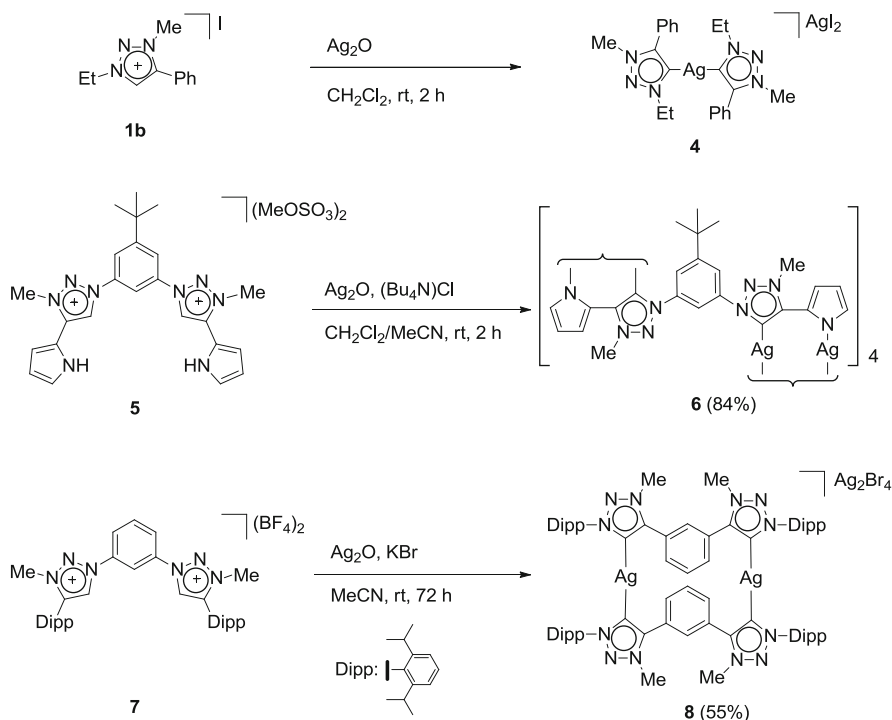
Scheme 2 Direct metallation of 1,2,3-triazolium salts with $\text{Pd}(\text{OAc})_2$

Different research groups have pioneered the synthetic routes (A–C) outlined above to prepare triazolylidene metal complexes from 1,2,3-triazoles. Albrecht described the first triazolylidene metal complex in 2008 using the *N*-alkylation/metallation route and also paved the way for the application of transmetalation reactions to 1,2,3-triazolylidene complexes [9]. Bertrand, on the other hand, succeeded to isolate and characterize the first free triazolylidene, demonstrating its coordination with transition metal complexes [2]. Finally, Gandelman recognized C5-metallated 1,2,3-triazolide anions as potential precursors of triazolylidene complexes by *N*-alkylation of the heterocyclic ring [10].

In the next Sects. (2.1)–(2.4) some illustrative synthetic examples to prepare 1,2,3-triazolylidene metal complexes from 1,2,3-triazoles are presented, focusing the discussion on their scope and limitations.

2.1 Direct Metallation of 1,2,3-Triazolium Salts

A direct, albeit not straightforward, method to form triazolylidene complexes involves the metallation of triazolium salts employing metals with basic ligands. For example, when the thermally induced metallation of triazolium salts **1** is carried out with $\text{Pd}(\text{OAc})_2$, a mixture of products is obtained comprising the dimeric monocarbenes **2** and biscarbenes **3**, the latter as *cis/trans* and *syn/anti* isomers (Scheme 2) [9, 11]. Sequential extraction and fractional crystallization of the reaction products derived from the triazolium salt **1b** allowed for isolating the corresponding pure complexes **2b**, *trans-3b*, and *cis-3b* (Similar mixtures of dimetallic and monometallic complexes have been reported in the palladation of imidazolium salts: [12]). Attempts to improve the reaction selectivity by adding an excess of iodide ligand (KI) or a base (NaOAc) resulted in a significant increase of the ratio of the dimeric complexes **2** (up to 8:1), but alternative attempts to improve



Scheme 3 Metallation of 1,2,3-triazolium salts to silver triazolyldene complexes with Ag_2O

the ratio of biscarbenes **3** failed. Luckily, applying a two-step transmetallation route provided more successful results (see Sect. 4.2).

Metallation at the C5 position of triazolium cations can be conducted under milder conditions with Ag_2O following the method developed by Lin for 1,3-imidazolium salt [13]. The silver *N*-heterocyclic carbene complexes can be obtained as ionic and neutral compounds. Depending on the solvent employed, the metal to triazolium salt molar ratio and the presence of additive salts (e.g., KBr, Bu_4NCl , etc.), the silver complexes may present a large variety of structures. For example, the metallation of the triazolium salt **1b** with Ag_2O at room temperature yielded exclusively the cationic biscarbene **4**, which slowly decomposed in solution but was stable enough to be characterized by NMR and MS analysis (Scheme 3) [9]. Most silver triazolyldene complexes are unsuitable for isolation and purification using standard laboratory protocols, but their formation can be easily accessed by NMR analysis checking the disappearance of the low field triazolium H5 proton, the downfield shift of the C5 signal in the ^{13}C NMR spectrum and the coupling of the latter with ^{107}Ag .

Aided by the steric effects of their bulky ligands, only two stable silver triazolyldene complexes, **6** and **8**, have been isolated to date and their structures determined by X-ray crystallography (Fig. 3) [14, 15]. In one complex, derived

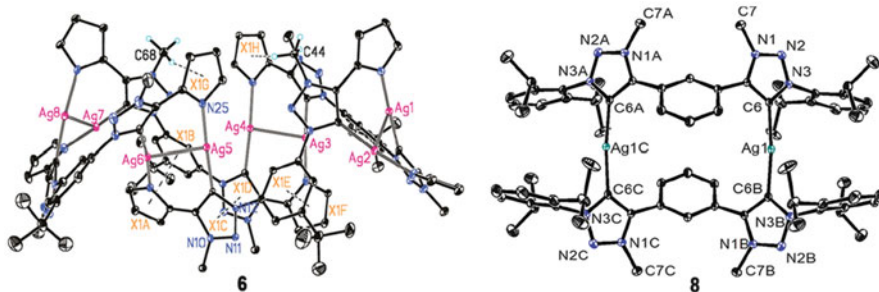


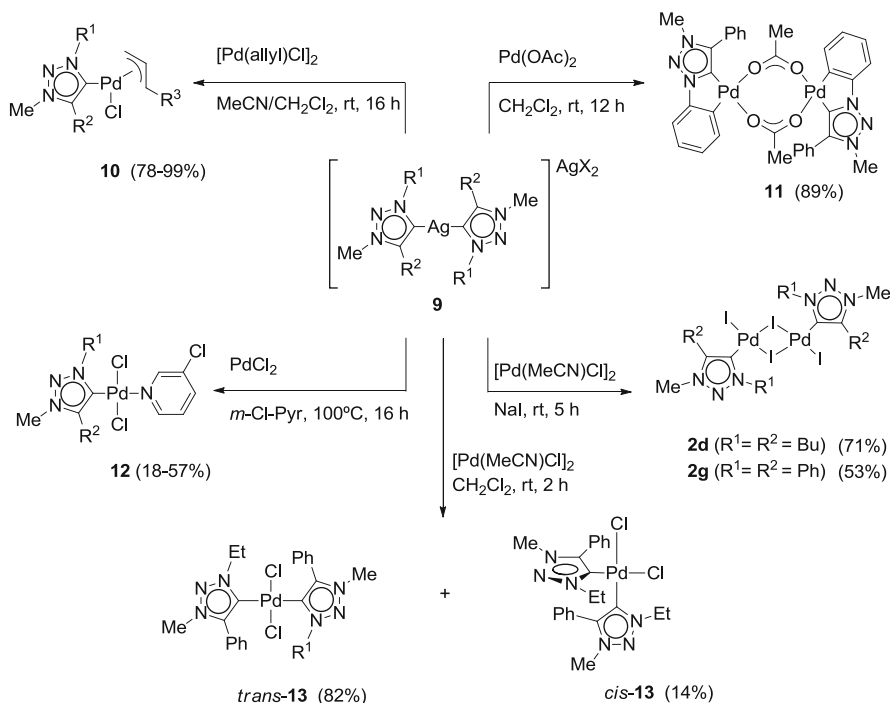
Fig. 3 X-ray structures of the neutral octanuclear silver triazolyldiene **6** and the cationic dinuclear carbene complex **8**. Figure partially reprinted from [14, 15], © 2011, 2012 ACS

from the pyrrole-functionalized ditriazolium salt, **6**, each silver cation is bound to one triazolyldiene and one deprotonated pyrrolyl ligand in a *trans* configuration. Due to the four bonding sites of each ligand precursor, a macrocyclic structure is obtained, comprised of four ligands, eight Ag(I) centers, and various weak interactions, including Ag–Ag contact pairs. In contrast to this formally neutral complex, the silver carbene **8** is cationic and features two Ag biscarbene moieties. This complex is derived from the related ditriazolium salt **7** that lacks additional stabilizing pyrrole substituents.

As mentioned above, the direct metallation approach to prepare 1,2,3-triazolyldiene metal complexes from triazolium salts is often thwarted by the obtention of complex reaction mixtures when the transformation needs to be carried under thermal conditions. Furthermore, there are only a limited number of metal complexes available with basic ligands strong enough to promote the in situ deprotonation of the cationic heterocycle. Transmetalation of silver carbene complexes offers a solution to these drawbacks and is currently the most widely employed method to prepare triazole carbene complexes.

2.2 Transmetalation of 1,2,3-Triazolyldiene Complexes

Transmetalation of silver carbenes with suitable transition metal complexes, specially bridged dimeric species (e.g., $[\text{Rh}(\text{cod})\text{Cl}]_2$, $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$, $[\text{Ru}(\text{cym})\text{Cl}_2]_2$, or PdCl_2), provides a general and clean metal exchange procedure working under mild reaction conditions. It also allows for the preparation of otherwise inaccessible 1,2,3-triazol-5-ylidene metal complexes. The transformation is achieved in two steps, preparing first the silver carbene as outlined in Sect. (2.1) and then performing the in situ carbene transfer to another metal. Successful triazolyldiene transmetalations have been achieved with a variety of transition metals including Au(I), Cu(I), Pd(II), Rh(I), Ir(I), and Ru(II). The whole process is thermodynamically favored by the addition of halide salts (typically R_4NX) or by the selection of transfer metal

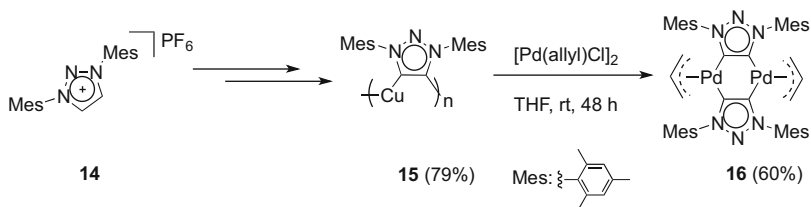


Scheme 4 Ligand dependence on transpalladation reaction products from silver triazolylidene complex **9**

complexes containing halide ligands (e.g., Pd(MeCN)Cl_2 , Pt(cod)Cl_2 , or CuCl) to promote the precipitation of AgX salts.

As outlined by Albrecht, the choice of metal precursor and metallation procedure determines the selectivity of product formation during the transmetalation of silver carbene complexes [16, 17]. For example, transpalladation of the silver carbene **9** with a dimeric palladium chloride source, such as $[\text{Pd(allyl)Cl}]_2$ or PdCl_2 , in the presence of another coordinating ligand affords the monocarbene triazolylidene complexes, **10** and **12** (Scheme 4). Addition of Pd(OAc)_2 to the silver carbene complex selectively affords the dimeric palladium species **11** [18]. It is notable that cyclopalladation of the ligand occurs in this case (see Sect. 5.2 for more details). In contrast, $\text{Pd(RCN)}_2\text{Cl}_2$ favors the formation of the biscarbenes, *trans*-**13** and *cis*-**13**, with the *trans* isomer as the major species. Both forms exist as *syn* and *anti* conformers. Finally, performing the carbene transfer in the presence of NaI selectively yields the dimeric palladium species **2** with bridging iodide groups.

Transmetalation by using coinage metal complexes other than silver is well documented [19], and Bertrand has described recently the first extension of this concept to 1,2,3-triazol-4,5-diylidenes (Scheme 5) [20]. Accordingly, the requisite polymeric copper dicarbene complex **15** was obtained in 79% yield by sequential



Scheme 5 Transmetalation reaction of copper 1,2,3-triazoldiylidene complexes

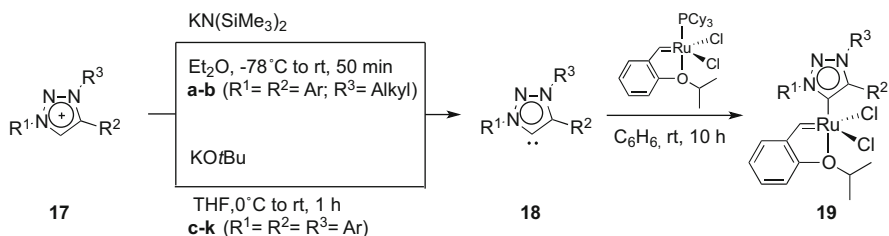
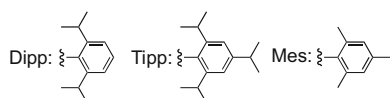
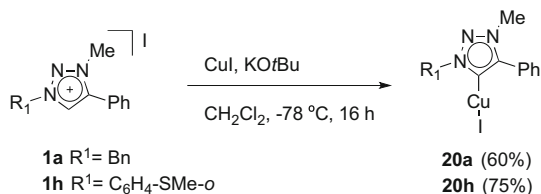
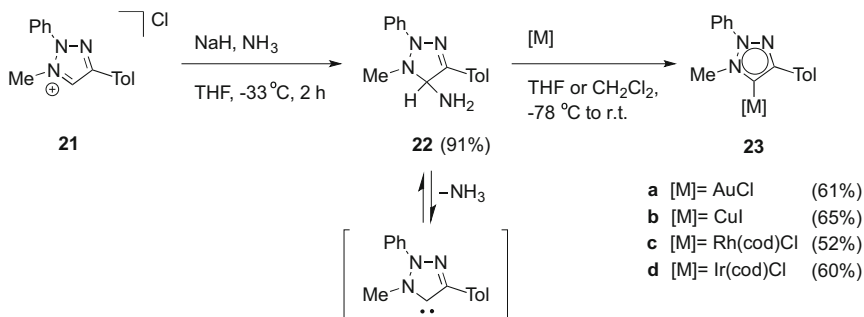
deprotonation and metallation with CuCl of the triazolium salt **14**. The latter was reacted with dimeric allylpalladium chloride to give the dimetallic dicarbene complex **16** in 60% yield (see also Sect. 8).

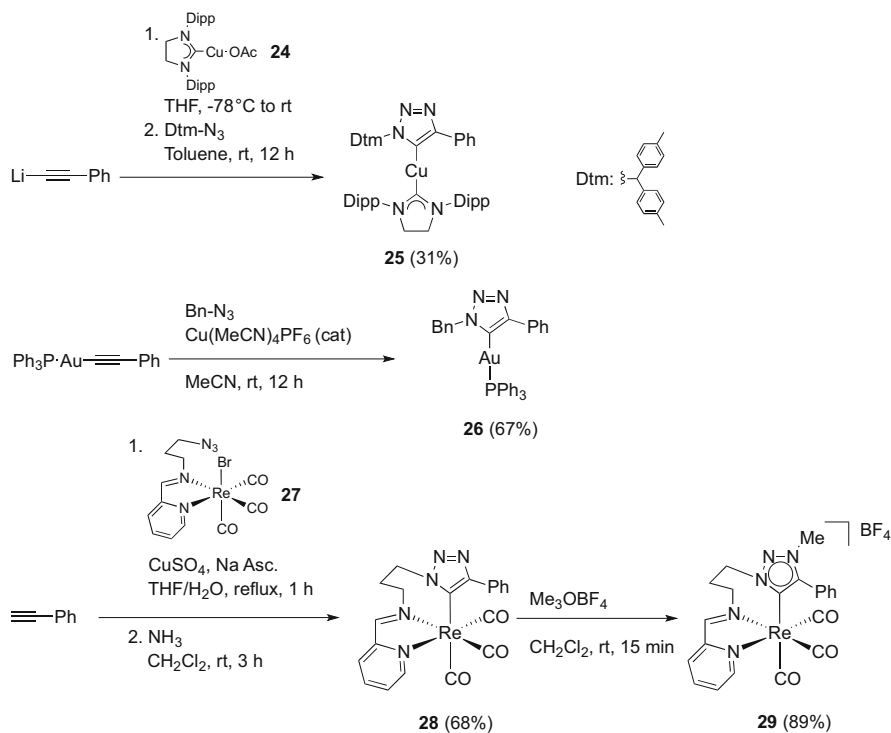
2.3 Metallation of Free 1,2,3-Triazole Carbenes or Carbene Adducts

Conceptually, the simplest and more elegant method to obtain triazolylidene metal complexes involves the preparation and isolation of free carbenes, followed by complexation with suitable metal carriers. Bertrand and coworkers have implemented this idea to the synthesis of ruthenium complexes **19** [3]. First, they prepared the free 1,2,3-triazolylienes **18** by deprotonation of the triazolium salts **17** using $\text{KN}(\text{SiMe}_3)_2$ or $\text{KO}t\text{Bu}$ as non-nucleophilic bases (Scheme 6).

The deprotonation of N3-alkyl triazolium salts **17a–b** required the strong base $\text{KN}(\text{SiMe}_3)_2$ ($\text{p}K_{\text{a}} = 26$), whereas N3-aryl carbenes **18c–k** were better obtained with the weaker base $\text{KO}t\text{Bu}$ ($\text{p}K_{\text{a}} = 22$) [2, 3]. However, both methods failed to form the free carbenes derived from N1, N3-dialkyl triazolium ions. To overcome the operational difficulties arising from the isolation and manipulation of free triazole carbenes, the deprotonation-metallation sequence can be accomplished in a one-pot operation. Sarkar and coworkers [21] have successfully implemented this method in the formation of triazolylidene copper(I) complexes **20** from the triazolium salts **1** with $\text{KO}t\text{Bu}$ base and CuI at low temperature (Scheme 7). Many mechanistic details of this transformation (e.g., direct C5-H proton abstraction versus $\text{Cu}(\text{O}t\text{Bu})$ formation) remain unexplained [2].

When applying conventional deprotonation routes to 1,2,4-trisubstituted triazolium salts **21**, only mixtures of decomposition products were isolated, or, in the presence of suitable metal precursors, very small amounts of metal carbenes were formed (Scheme 8). Kühn reported a solution to this problem by trapping in situ the free carbenes as ammonia adduct (**22**), which can be safely stored in THF at -30°C for several months without decomposition. The same author has demonstrated that this carbene adduct undergoes direct metallation reactions with Ir(I), Rh(I), Cu(I), and Au(I) complexes, resulting in 1,2,4-trisubstituted triazolylidene complexes **23** [22].

**18a** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{Me}$) (55%)**18b** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = i\text{Pr}$) (39%)**18c** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{Dipp}$) (90%)**18d** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Mes}$; $\text{R}^3 = \text{Dipp}$) (77%)**18e** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Dipp}$) (88%)**18f** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Tipp}$; $\text{R}^3 = \text{Dipp}$) (99%)**18g** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = t\text{Bu}$; $\text{R}^3 = \text{Dipp}$) (69%)**18h** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Cy}$; $\text{R}^3 = \text{Dipp}$) (69%)**18i** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{OEt}$; $\text{R}^3 = \text{Dipp}$) (83%)**18j** ($\text{R}^1 = \text{Mes}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{Mes}$) (98%)**18k** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Mes}$) (99%)**19c** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{Dipp}$) (49%)**19d** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Mes}$; $\text{R}^3 = \text{Dipp}$) (21%)**19f** ($\text{R}^1 = \text{Dipp}$; $\text{R}^2 = \text{Tipp}$; $\text{R}^3 = \text{Dipp}$) (50%)**19j** ($\text{R}^1 = \text{Mes}$; $\text{R}^2 = \text{Ph}$; $\text{R}^3 = \text{Mes}$) (17%)**Scheme 6** Preparation of free triazolylidenes and further metallation to ruthenium(II) complexes**Scheme 7** Direct cupration of 1,2,3-triazolium salts in the presence of KOtBu base**Scheme 8** 1,2,4-Trisubstituted triazolylidene complexes from the ammonia-carbene adduct **22**

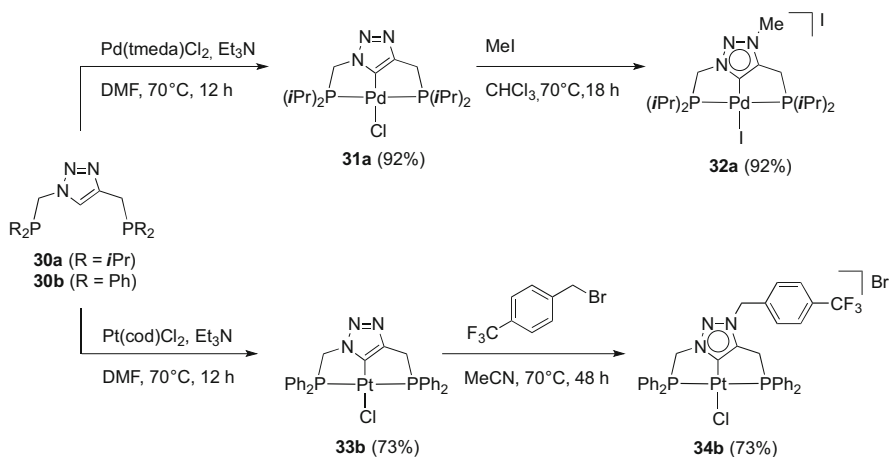


Scheme 9 Preparation of copper(I) triazolidine complexes from CuAAC reactions

2.4 N-Alkylation of 1,2,3-Triazolidine Carbanions

Straub and coworkers succeeded to isolate the first stable copper(I) 1,4-disubstituted-1,2,3-triazolidine complex **25** by reacting a bulky NHC-stabilized copper(I) acetylide, generated in situ from lithium phenylacetylide and the carbene cuprate **24**, with azido-di(4-tolyl)methane in toluene (Scheme 9) [23]. Complex **25** was stable in air and water, and its molecular structure was confirmed by X-ray crystallography. The copper(I) 1,2,3-triazolidine species is presumed to be an intermediate in the catalytic cycle of the CuAAC reaction. Straub also showed that protonolysis of the triazolidine cuprate **25** with acetic acid in dichloromethane at room temperature leads to the corresponding 1,4-disubstituted-1,2,3-triazole and the NHC-Cu-OAc complex **24**.

Gray has synthesized a family of stable gold(I) 1,4-disubstituted-1,2,3-triazolidine complexes (e.g., **26**) in moderate to good yields using the copper(I)-catalyzed [3+2] cycloaddition reaction of gold(I) alkynyls with benzyl azide [24]. The reaction protocol tolerated a broad range of functionalities on the alkynyl moiety, and the resulting complexes were air and water stable. The gold(I)-1,2,3-triazolidine

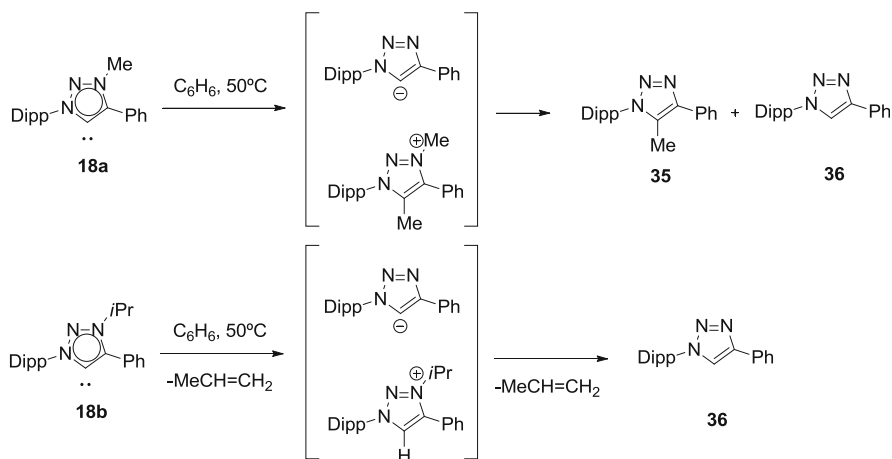


Scheme 10 Triazolylidene metal complexes by alkylation of metal triazolidine precursors

complexes of the type **26** were luminescent and displayed both singlet- and triplet-state emissions. Neither the copper complexes **25** nor the gold complexes **26** were submitted to *N*-alkylation to prepare the corresponding MIC complexes. In contrast, Miguel and coworkers have reported the first example of the preparation of a triazolylidene complex **29** taking advantage of a remarkable CuAAC reaction between phenylacetylene and the azide **27**, which involved a spontaneous copper to rhenium transmetalation during the formation of the triazolidine anion complex **28** [25]. Selective *N*-alkylation of the triazole ring in **28** with Me_3OBF_4 afforded the MIC complex **29**.

Gandelman and coworkers have taken advantage of the particular chelating ability of triazole pincer ligands **30** to promote their facile C5 metallation using tertiary amine bases and suitable palladium(II) and platinum(II) complexes, avoiding in this way the in situ preparation of the 1,2,3-triazolidine core with a CuAAC reaction from alkynes and azides (Scheme 10) [10, 26–28].

Triazolidine *N*-alkylation of **31a** and **33b** with methyl iodide and *p*-trifluoromethylbenzyl bromide, respectively, led to the formation of the triazolylidene carbenes **32a** and **34b** in 92% and 73% yields. Both complexes showed a square-planar geometry around the Pd(II) and Pt(II) metals as ascertained from their X-ray crystal structures. Furthermore, the C5–Pd bond length shortened from 1.929 Å in **31a** to 1.902 Å in **32a**, indicating the increased contribution of carbene character of this bond. ^{195}Pt NMR also proved useful in observing changes in the electronic environment of the platinum center. Alkylated cationic complex **34b** exhibited a double doublet-platinum resonance due to its coupling to two nonsymmetric phosphines at $\delta = -4,347$ ppm. This was an effective upfield shift of approximately 100 ppm relative to starting neutral complex **33b**.



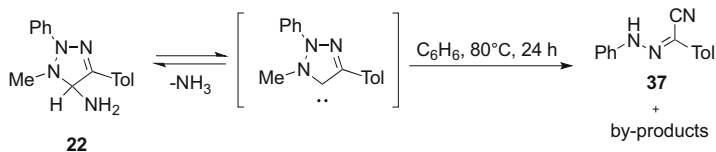
Scheme 11 Thermal decomposition of 3-alkyl-1,4-diaryltriazolylienes

3 Stability and Reactivity of Metal Triazolylidene Complexes

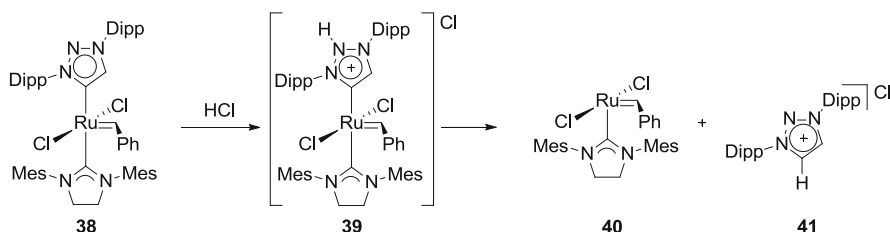
This section covers the transformations of free 1,2,3-triazole carbenes and/or their metal complexes into noncarbene compounds. Related transformation preserving the C5–M carbene metal bond, such as ligand exchange reactions or cyclometallation reactions, is covered in Sect. 5.

3.1 Thermal Stability of Free Triazolylienes

Thermal stability of free triazole carbenes is strongly dependent on the steric bulkiness of the ring substituents [2, 3]. For example, in the solid state, with the exclusion of oxygen and moisture, free 3-methyl-1,2,3-triazol-5-ylidene **18a** (m.p. $50\text{--}52^\circ\text{C}$) remained stable for several days at -30°C and for a few hours at room temperature (Scheme 11). By contrast, **18b** (m.p. $110\text{--}112^\circ\text{C}$), bearing a bulkier N3-isopropyl substituent, was significantly more stable showing no sign of decomposition after 3 days at room temperature in the solid state. Upon heating in a benzene solution for 12 h at 50°C , **18a** decomposed to give a mixture of the C5-methylated triazole **35** and the protonated analog **36**. The methylated product **35** could result from a nucleophilic attack of the carbon lone pair of **18a** on the methyl group of a second molecule of **18a**. In agreement with this hypothesis, MIC **18b**, which contains the less-electrophilic isopropyl group at the N3 position, would give a propylene elimination reaction to provide only compound **36**.



Scheme 12 Thermal decomposition of 1,2,4-trisubstituted ammonia-triazolylidene adduct **22**



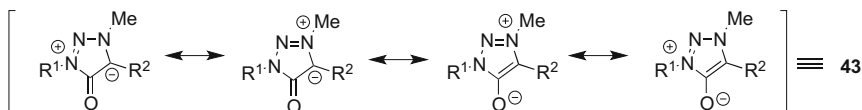
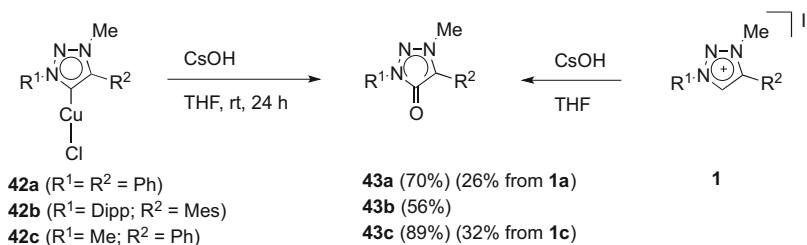
Scheme 13 Protonolysis of a mixed ruthenium(II) triazole(MIC)-imidazole(NHC) complex

Analogous nonmesoionic 1,2,4-trisubstituted free carbenes are less stable than their mesoionic 1,2,3-substituted triazolylidene counterparts and cannot be isolated. However, their ammonia-carbene adducts (e.g., **22**) were stable in C₆D₆ solution for days at room temperature and slowly decomposed only when heated to 80°C for 24 h (Scheme 12). Hydrazonoyl cyanide **37** could be isolated from the resulting mixture. Interestingly, the methyl group was absent in **37**, suggesting intermediate carbene formation and subsequent alkyl rearrangement [22].

3.2 Protonolysis of Triazolylidene Complexes

Triazolylidene–metal bonds (C5–M) have been reported to be stable under acidic conditions. For example, palladium complexes **2f–g** (see Scheme 2) survived the exposure to HI for several days without any degradation [11]. Likewise, the iridium complexes **82** (see Scheme 36, Sect. 5.2) tolerated aqueous 1 M HCl for several days [29].

Grubbs and Bertrand have studied the Brønsted acid-promoted protonolysis of the ruthenium complex **38** containing an unhindered 5H-unsubstituted triazolylidene (MIC) and an *N*-heterocyclic carbene (NHC) (Scheme 13) [30]. The cleavage of the Ru–MIC bond was observed to generate an extremely active metathesis catalyst **40** and the triazolium salt **41**, demonstrating that a MIC ligand may act as a leaving group, allowing an otherwise inactive complex **38** to enter the metathesis catalytic cycle. Previously reported density functional theory calculations suggest that N2 nitrogen atom on the MIC ligand **38** has the second-highest proton affinity after the carbene itself [3]. Thus, it is likely that protonolysis could involve the triazolium salt **39**.



Scheme 14 Oxidative transformation of copper(I) triazolylidene complexes

3.3 Oxidation

The only example of the oxidative transformation of triazole carbenes to mesoionic sydnone analog compounds **43** has been reported by Albrecht, starting from the corresponding triazolylidene cuprous salts **42** and CsOH (Scheme 14) [31]. Identical products are formed while treating the triazolium salts **1** with the same hydroxide, albeit in lower yields and contaminated with minor amounts of the de-methylated triazoles. The reaction from the copper complex presumably occurs via reductive carbene hydroxide elimination from a putative $[\text{Cu}(\text{triazolylidene})\text{OH}]$ intermediate.

The synthetic methodology is remarkably general and provides facile access to a wide range of mesoionic compounds that have potential in their own right, e.g., as new structural motifs in active pharmacological ingredients and also as a new class of ligands with a high degree of electronic flexibility.

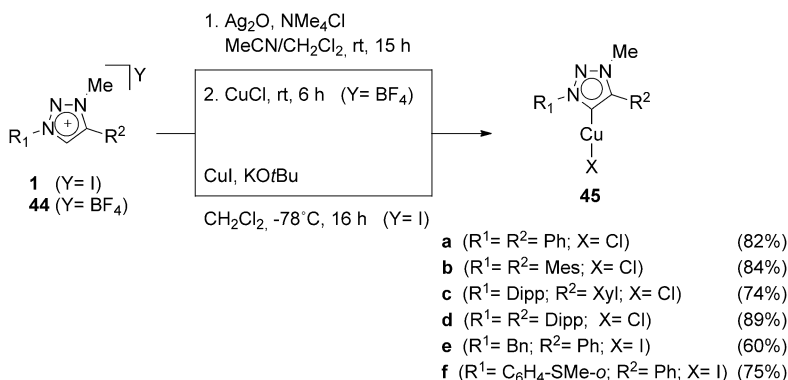
The next Sects. (4)–(8) collect the synthesis, main structural details, and chemical applications of the different triazolylidene metal complexes **A–J** (Fig. 2) classified following the different transition metal groups.

4 Monodentate 1,2,3-Triazolylidene Complexes

4.1 Monocarbene Complexes (Type A)

4.1.1 Copper

Fukuzawa and coworkers have described the first synthesis of copper complexes **45a–d** bearing a 1,2,3-triazole carbene ligand [32, 33]. Simultaneously, Sarkar prepared copper complexes **45e–f** in a different way [21]. Complexes **45** are



Scheme 15 Synthesis of monodentate copper(I) triazolylidene complexes

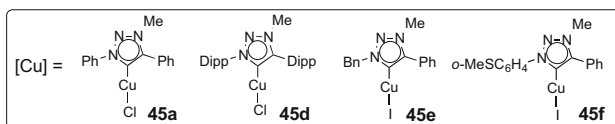
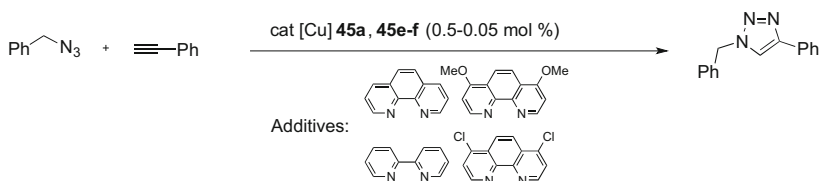
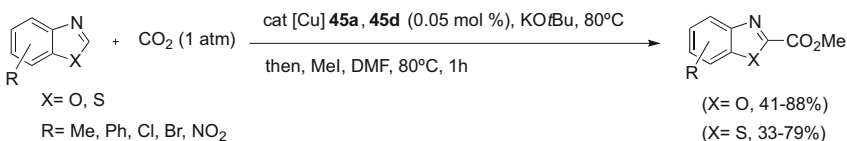
versatile catalysts for the CuAAC “click” cycloaddition of a wide range of alkynes and azides and for the direct carboxylation of benzoxazoles and benzothiazoles.

The air-Stable 1,2,3-triazol-5-ylidene-copper(I) complexes **45a–d** were obtained treating the corresponding triazolium tetrafluoroborate salts **44** with Ag_2O and tetramethylammonium chloride, followed by transmetalation with CuCl at room temperature. Complexes **45e–f**, on the other hand, were prepared by direct deprotonation-metallation of the triazolium iodide salts **1** with KOtBu and CuI at low temperature (Scheme 15).

Cuprous triazolylidene complexes **45** showed characteristic signals attributable to the metal-bonded carbene carbon around 160–170 ppm in the ^{13}C NMR spectrum. X-ray analysis of a single crystal of complex **45c** showed that bond distance and angles were similar to those in the previously reported copper imidazole carbene complex $\text{Cu}(\text{ImPr})\text{Cl}$ [34]. The C–Cu–Cl and C–Cu–I angles in **45c** and **45f** were linear and the Cu–Cl and Cu–I bond lengths were 2.115(15) Å and 2.236(2) Å, respectively. Lastly, the C–Cu bond lengths for **45c** and **45f** were 1.879(5) Å and 1.89(1) Å, respectively.

Triazolylidene complexes **45** acted as efficient catalysts for azide-alkyne [3+2] cycloaddition reactions at very low loads of catalyst (typically 0.5–0.05 mol%) (Scheme 16) [32].

Functional groups such as alcohols, esters, and pyridines were well tolerated, while primary amines containing alkynes were not coupled efficiently and produced mixtures. The best of the series, complex **45a**, was more active than 2-imidazolylidene copper analogs in a test reaction and performed well in reactions where classical catalysts tend to fail. For example, the coupling of sterically bulky alkynes with bulky azides (e.g., Dipp–CCH with Dipp– N_3) proceeded with high conversion, albeit after long reaction times (18 h). Gautier and coworkers have reported that the scope of the Cu(I) (MIC) catalysts **45a–f** can be extended by adding aromatic *N*-donor ligands such as 1,10-phenanthroline or 4,7-dichloro-1,10-phenanthroline [35]. Using the latter additive, the solubility of the catalyst was

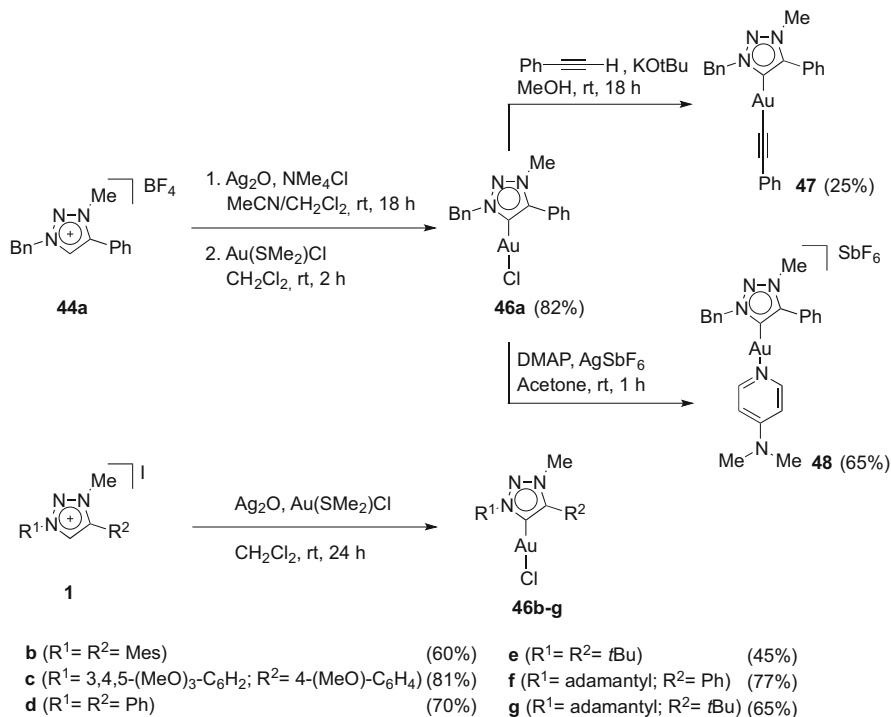
**CuAAC test reaction****Direct carboxylation of benzoxazoles and benzothiazoles****Scheme 16** CuAAC and direct carboxylation reactions catalyzed with copper(I) MIC complexes

improved in various solvents and the cycloaddition rate increased dramatically. Fukuzawa also performed the direct transformation of benzoxazoles and benzothiazoles into the corresponding 2-methoxycarbonyl heterocycles using carbon dioxide as the electrophile under low loads of copper triazolyldene complexes **45a** and **45d**. The same author developed a similar method for the C-thiolation of benzothiazoles and benzoxazoles with thiophenols and alkylthiols [36].

4.1.2 Gold

Crowley and coworkers have prepared several triazolyldene gold complexes and have demonstrated their usefulness as highly active catalyst precursors for carbene insertion and cyclization reactions [37]. For example, the triazolium salt **44a** was readily metallated with Ag_2O and transmetallated with $\text{Au}(\text{SMe}_2)\text{Cl}$ to provide the gold(I) 1,2,3-triazolyldene chloride complex **46a** in 82% yield. The chloride anion of **46a** could be replaced by other ligands to give the neutral phenylacetylide **47** or the cationic N,N' -dimethylaminopyridine complex **48** (Scheme 17). In a similar development Albrecht prepared the gold(I) triazolyldene complexes **46b–g** starting from triazolium iodides **1** rather than tetrafluoroborate salts, avoiding the use of alkylammonium salt additives [38]. Complex **46a** was air and moisture stable in solution and in the solid state.

Gold(I) 1,2,3-triazolyldene complexes **46–48** showed typical chemical shifts of the carbene carbons between δ_{C} 174 and 155 ppm in the ^{13}C NMR spectra, similar to other reported 1,2,3-triazolyldene metal carbenes, but significantly lower than



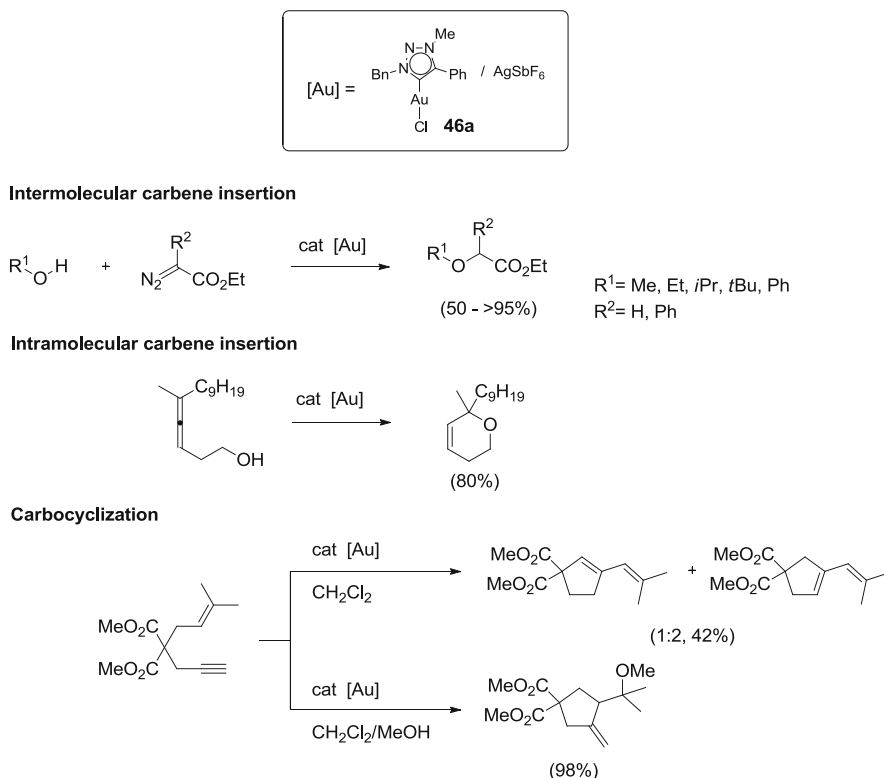
Scheme 17 1,3,4-Trisubstituted gold(I) triazolyldiene complexes

those observed for previously reported gold(I) imidazole carbene complexes [39, 40]. X-ray crystal structure of **46–48** showed gold(I) ions coordinated in a linear fashion with L–Au–C bond angles ranging from 173.6° to 177.2°. The Au–C and Au–L bond lengths were similar to those reported for other gold(I) imidazole carbene complexes [39–42].

Triazolyldiene gold complex **46a** precatalyst in combination with AgSbF₆ was a highly active catalyst for carbene insertion and cyclization reactions (Scheme 18).

For example, the cationic auric catalyst generated in situ from **46a** promoted the insertion of the carbene derived from α -azidoesters into O–H bonds of primary, secondary, and tertiary alcohols. Insertion into phenolic O–H bonds or into N–H bond of aniline was less efficient. Likewise, using larger carbene precursors than ethyl diazoacetate (e.g., ethyl α -diazophenylacetate) was not clean, though still feasible. Similar intramolecular insertion reactions were also catalyzed by the complex **46a**/AgSbF₆ system when using allenes instead of diazo precursors of carbene. Finally, the carbocyclization of enynes has also been demonstrated using the same catalyst.

Kühn and coworkers have synthesized a series of gold(I) complexes coordinated to “normal” 1,2,3-triazolyldiene ligands and examined their feasibility in catalysis (Scheme 19). Accordingly, chloride complexes **50** were prepared using the

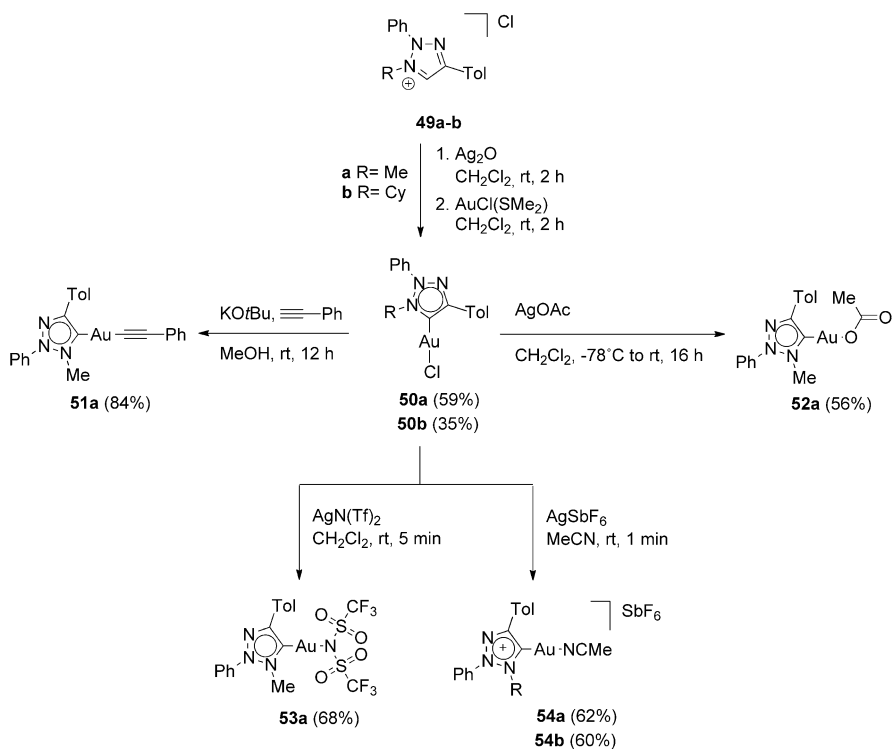


Scheme 18 Gold(I) triazolylidene-catalyzed carbene insertion and carbocyclization reactions

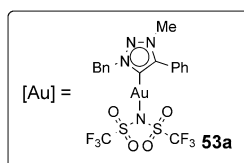
transmetallation procedure from the triazolium salts **49** [43]. Different gold(I) compounds **51–54** with a variety of ligands were synthesized in order to avoid the use of silver salt additives for halide dissociation during catalysis.

The X-ray crystal structure of **50a** showed in the unit cell a close Au–Au contact of 3.499 Å, which is well within the range of typical aurophilic interactions [44]. The Au–Cl bond length of **50a** was 2.290(1) Å, comparable to bond lengths observed in the related triazolylidene compound of Lee and Crowley (2.2940(10) Å), in [Au(ImPr)Cl] (2.2698(11) Å), or in [Au(ImCy)Cl] (2.306(3) Å, 2.281(3) Å) described by Nolan [45].

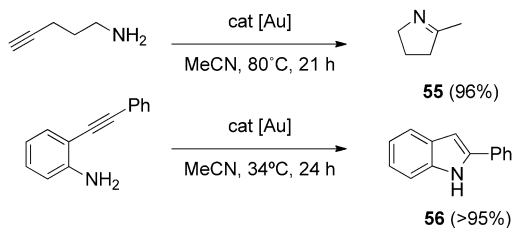
Complexes **50–51** were air and moisture stable, compounds **52–53** were stable for hours under similar conditions, and complexes **54a–b** appear to be less stable, but were storable in the solid under argon at low temperature. All synthesized compounds **50–54** were screened as catalysts for the hydroamination of 4-pentyn-1-amine, to yield the ring-closing product **55** (Scheme 20). The catalyst **51a** turned out to be the least active, followed by complexes **50b**, **52a**, and **50a**. Better-performing precatalysts contained more labile substituents, such as acetonitrile (**54a–b**) and, especially, triflamide **53a** which catalyzed the formation of the



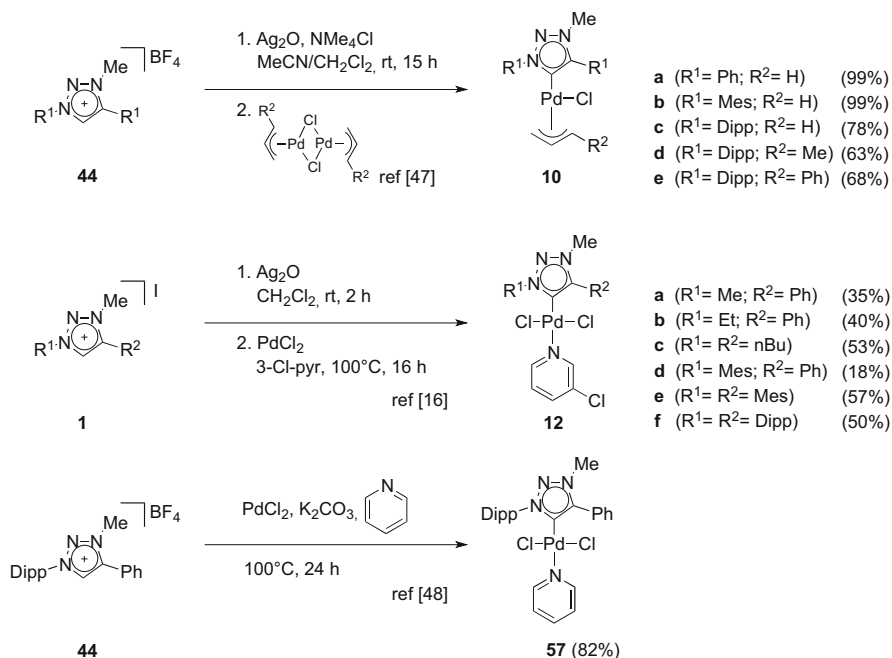
Scheme 19 Synthesis of gold(I) 1,2,4-substituted triazolylidene complexes



Intramolecular hydroamination of alkyne-amines



Scheme 20 Gold(I) triazolylidene-catalyzed dehydroamination of alkyne amines



Scheme 21 Synthesis of palladium(II) triazolylidene complexes

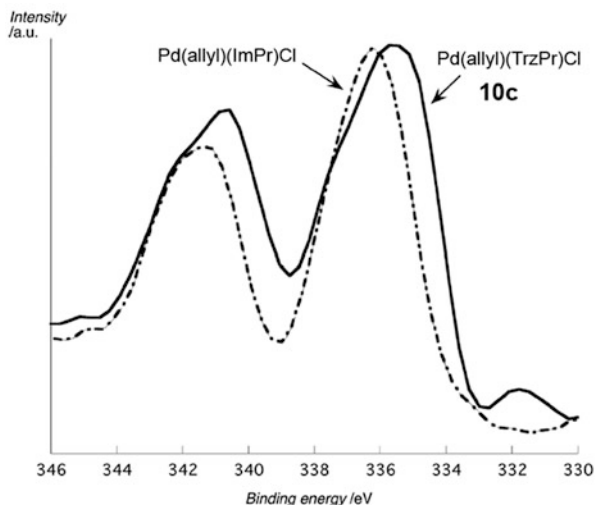
aliphatic ring-closing imine **55** in a 96% yield after 21 h in refluxing acetonitrile. Triazolylidene complex **53a** also catalyzed the hydroamination reaction of 2-(2-phenylethynyl)aniline containing an internal alkyne to the indole **56** in virtually quantitative yield at room temperature. Compounds **54** seemed at first most promising for catalysis applications due to their rather labile acetonitrile substituent, but in practice they were much less active than complex **53a**.

4.1.3 Palladium

Palladium currently enjoys preeminent status in cross-coupling reactions. Hence, it is not surprising that many triazolylidene palladium complexes have been investigated as catalyst precursors for Suzuki–Miyaura cross-coupling. In particular, the superior donor ability of triazolyldenes compared to phosphines and imidazole carbenes was expected to improve the aryl halide insertion to palladium(0) intermediates, in less reactive aryl chlorides. Several monodentate monomeric MIC-palladium complexes prepared to this end are shown in Scheme 21.

Fukuzawa and coworkers [46] have prepared Pd(II) monotriazolylidene complexes **10** considering to be more preferable active catalysts than the bis (triazolylidene)metal complex analogs. Complexes **10a–e** were prepared following

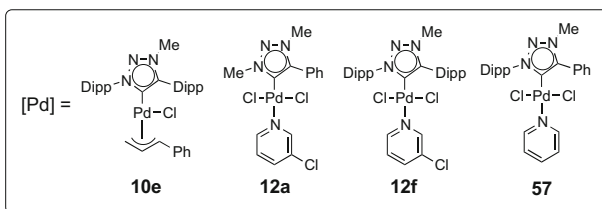
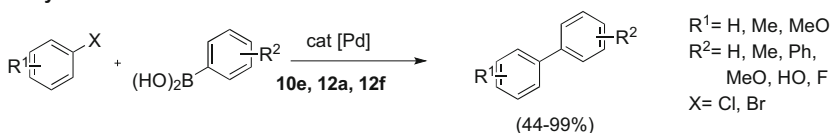
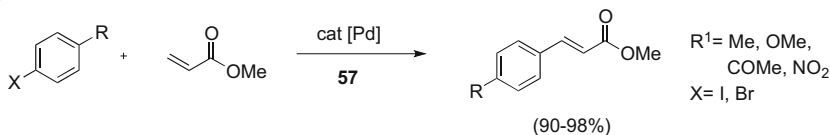
Fig. 4 XPS spectra (palladium 3d level) for **10c** (solid line) and (allyl)(ImPr)PdCl. Figure partially reprinted from [46], © 2013 VCH



the transmetalation procedure with Ag_2O and $[\text{Pd}(\text{allyl})\text{Cl}]_2$ in CH_2Cl_2 at room temperature. Concomitantly, and inspired by the PEPPSI concept (pyridine-enhanced precatalyst preparation, stabilization, and initiation), Albrecht [16] synthesized the complexes **12** containing an easily cleavable 3-chloropyridine ligand by metallation of the triazole iodide salts **1** with Ag_2O and subsequent transmetalation in 3-chloropyridine as the solvent. The PEPPSI-type palladium complexes **12** were air- and moisture-stable solids. Finally, Crudden [47] synthesized the complex **57** by direct deprotonation-metallation of the triazolium tetrafluoroborate salt **44** with PdCl_2 in pyridine in the presence of potassium carbonate.

The strong donor properties of the triazole carbenes **10** were confirmed by X-ray photoelectron spectroscopy (XPS) (Fig. 4) [48, 49]. A comparison between the triazole carbene complex **10c** and a complex sterically identical to the imidazole complex, e.g., $\text{Pd}(\text{allyl})(\text{ImPr})\text{Cl}$, showed that the Pd 3d electron-binding energies in the former were 0.5 eV less than those in the latter [**10c**: 335.7 eV; $\text{Pd}(\text{allyl})(\text{ImPr})\text{Cl}$: 336.2 eV] indicating that the triazole carbene was a stronger donor than the imidazole analog.

Complexes **12b–d** were analyzed by single-crystal X-ray diffraction. In all instances, the ligands around the square-planar palladium center adopted the expected *trans* arrangement. The (MIC)C5-Pd bond length in all complexes was 1.96(1) Å, which is in line with those of related triazolylidene palladium complexes. The pyridine N–Pd bond length was weakly affected by the substitution pattern on the triazolylidene ligand and increased slightly in the series **12b** < **12c** < **12d**. The most pronounced distinction between the three complexes pertains to the different twist angle of the heterocycles out of the palladium coordination plane, with an almost perpendicular arrangement in **12d**, probably a direct consequence of the shielding properties of the *ortho*-methyl groups of the

**Suzuki-Miyaura****Heck****Scheme 22** Palladium(II) triazolylidene catalysts for Suzuki–Miyaura and Heck reactions

mesityl substituent. Finally, in the X-ray structure of complex **57** were observed several weak noncovalent C–H–Cl interactions occurring between one of the Pd-bound chlorine atoms and the *meta*-hydrogen of the pyridine of a neighboring molecule.

Complexes **10** and **12** have been investigated as Suzuki–Miyaura reaction catalysts (Scheme 22). Complex **10e**, containing Dipp wingtip groups and featuring a cinnamyl ligand, yielded the most active catalytic system. This complex showed high activity in the room temperature reaction with aryl chlorides; regardless of the electronic and steric properties of the substituents, it was effective in the reaction with sterically crowded arylboronic acids, and, furthermore, the reaction could be carried out with a low catalyst load (1–0.1 mol%). Sterically less demanding catalyst **12a**, on the other hand, gave moderate yields only with aryl bromides, whereas aryl chlorides led to conversions not exceeding 60%. Besides, the reaction outcome was very sensitive to the temperature due to the formation of heterogeneous Pd(0) colloids. Hong succeeded to alleviate this problem by using the more hindered catalyst **12f** [50]. The Heck reaction was finally screened for catalyst **57** to give aryl-substituted cinnamates from aryl bromides or iodides and methyl acrylate in excellent yields, following a heterogeneous reaction pathway.

Mechanistic studies conducted to compare precatalysts **12a** and **12b** using mass spectrometry (MS) and transmission electron microscopy (TEM) have revealed the formation of ligand-free Pd(0) clusters and particles in the 3–5 nm range under catalytic conditions, suggesting a heterogeneous process (Fig. 5) [16]. Formation of colloidal palladium may further explain the delicate role of the temperature, since

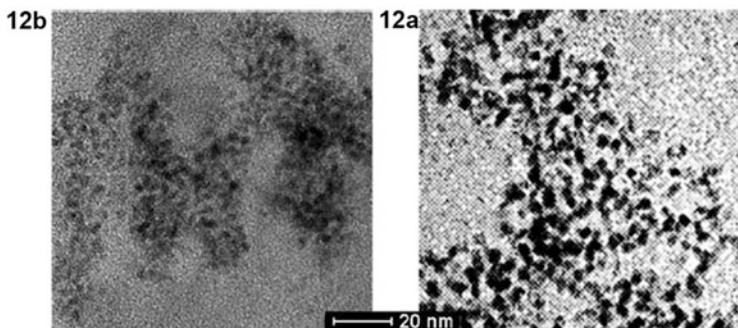
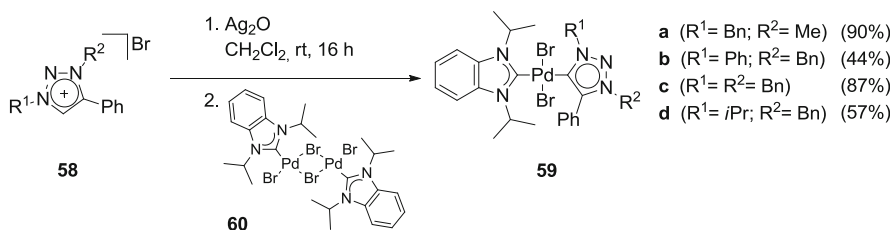


Fig. 5 TEM micrographs of post-reaction mixtures after the Suzuki–Miyaura reaction with **12b** and bromoanisole and **12a** and chlorobenzaldehyde. Figure partially reprinted from [15] © 2012 VCH



Scheme 23 Synthesis of palladium(II) (NHC)/(MIC)-mixed complexes

elevated temperatures accelerated colloid formation and eventually led to aggregation into large particles that cannot easily expel a palladium atom.

Some palladium(II) imidazole-triazole hetero-bis(carbene) complexes **59** have been designed and prepared by Huynh and coworkers to introduce a new method that employs a ^{13}C NMR spectroscopic evaluation of the relative donating ability of the triazole carbene ligand [51]. One-pot bridge-cleavage reactions of the dimeric benzimidazole complex **60** with two equivalents of triazole ligand precursor **58** and 1.2 equiv. of Ag_2O in CH_2Cl_2 yielded the desired hetero-bis(carbene) complexes **59** (Scheme 23).

In the ^{13}C NMR spectra of complexes **59a–d**, two carbene signals were observed as expected. The downfield signals ranging from 180.3 to 181.2 ppm were assigned to the imidazole carbene, whereas those ranging from 157.9 to 160.6 ppm were attributed to the 1,2,3-triazole-derived carbenes. It was empirically found that the ^{13}C carbenoid signal of the constant benzimidazole probe was sensitive to the transoid ligand L, whereby stronger donating ligands would lead to a more downfield shift [52–55]. An extension of this methodology to other ligand systems is shown in Fig. 6. A closer inspection of the $i\text{Pr}_2\text{-bimy}$ chemical shifts among the four triazolyldene complexes **59a–d** revealed increasing downfield shifts in the order **59b** (180.3 ppm) < **59a/59c** (180.8 ppm) < **59d** (181.2 ppm), reflecting a stepwise

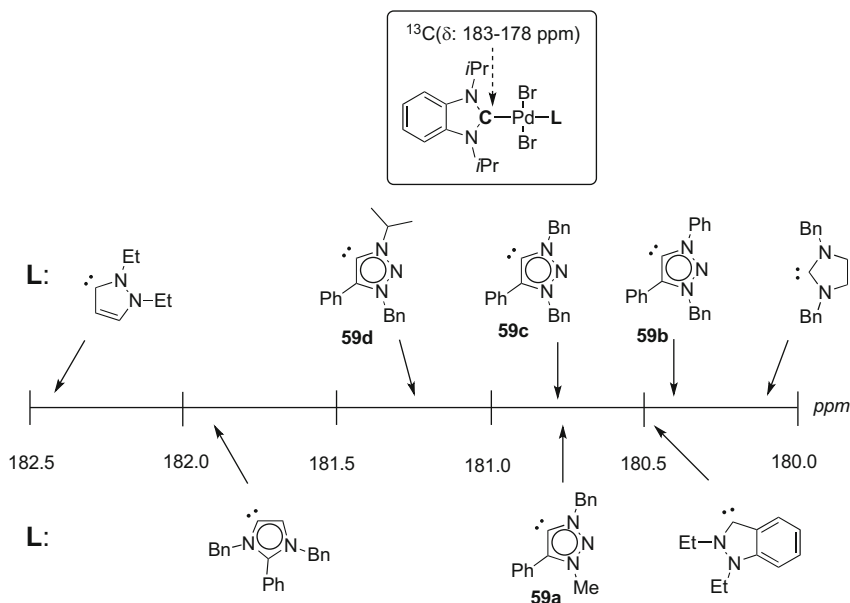


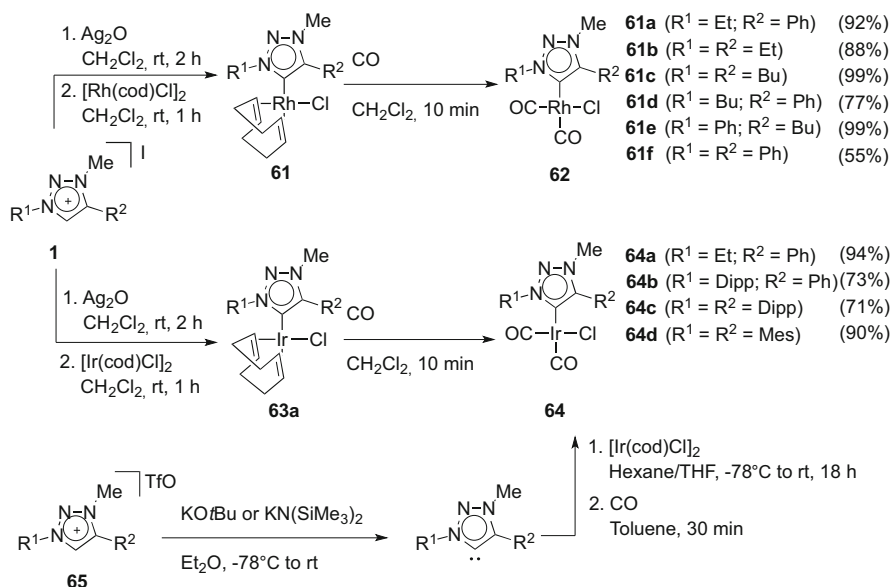
Fig. 6 Evaluation of the increasing donating ability of carbene ligands **L** by downfield shift of the benzimidazole carbene ^{13}C NMR signal (shown in ppm)

increase of the triazolylidene ligands donor ability. Because complexes **59b–d** differ only in the N1 substituent of the triazole ligand, the determined order also correctly reflected the increasing positive inductive effects of the groups $\text{Ph} < \text{Bn} < i\text{Pr}$. It must be highlighted that the lower sensitivity of common IR-based methodologies is not sufficient to discern electronic influences brought about by different substituents.

Finally, the mixed triazolylidene benzimidazolylidene complexes **59** were also used as precatalysts for the arylation of pentafluorobenzene with aryl bromides by direct C–H bond activation. The catalytic activity was higher at low catalyst loading (1–0.5%) than with higher concentrations of **59**. This behavior, together with the rather high operation temperature (120°C) and the incidental observation of palladium black, pointed to a possibly heterogeneous mechanism as established for the PEPPSI-type triazolylidene complexes **12** and **57**.

4.1.4 Rhodium and Iridium

Albrecht and coworkers [9, 11] have prepared several rhodium complexes **61–62** in order to evaluate the donating ability of triazolylidene ligands, first by NMR spectroscopy due to the $I = 1/2$ spin of ^{103}Rh and second by measuring the CO stretch vibration in the corresponding rhodium carbonyl complexes (translating into



Scheme 24 Carbonylation reaction of (cod) ligands in rhodium(I) and iridium(I) triazolylidene complexes

Tolman electronic parameters, TEPs). Accordingly, the rhodium complexes **61** were prepared using classical transmetallation procedures involving Ag_2O as a basic silver salt and $[\text{Rh}(\text{cod})\text{Cl}]_2$ as transmetallating agent (Scheme 24). Exposure of complexes **61** to a CO-saturated environment afforded the corresponding carbonyl analogs **62** in essentially quantitative yield [56, 57]. Twin iridium complexes **64** were also prepared in high yields using either the transmetallation procedure (**64a**) [2] or the free carbene trapping method for aryl-substituted complexes (**64b–d**) [9, 46].

The ^{13}C NMR chemical shift of the rhodium-bound triazolylidene carbon showed an apparent correlation with the nature of the wingtip group [11]. With alkyl wingtip groups, the doublet ($^1J_{\text{RhC}} = 46.5 \pm 3$ Hz for all complexes) appeared at highest field (δ_{C} 168.5 and 168.6 for **61b** and **61c**, respectively), while the presence of one phenyl group as in **61d** and **61e** induced a downfield shift (δ_{C} 170.4 for both complexes) when considering the $^1J_{\text{RhC}}$ coupling constant of rhodium with the *trans*-CO, an increase of $^1J_{\text{RhCO}}$ was observed upon reduction the wingtip donating ability.

The CO stretch vibrations occurred in the IR spectrum at 1,983 and 2,065 cm^{-1} for all complexes **62** except for **62f** ($\nu_{\text{CO}} = 1,988$ and 2,068 cm^{-1}). Depending on the applied linear regression [58, 59], these values translated into a TEP in the range 2,035–2,042 cm^{-1} . Because of the identical CO absorption energies, the calculated TEPs for the triazolylidene ligands in complexes **62b–e** were obviously the same,

which may indicate some limitation of this method for evaluating ligand donor properties [60–62]. TEP variations recorded for iridium-triazolylidene complexes **64** followed essentially the same trend of their rhodium analogs **62** [46].

4.1.5 Ruthenium

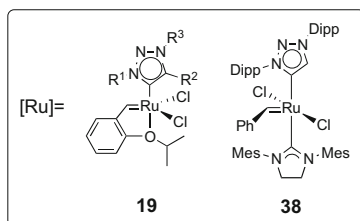
Bertrand and Grubbs have explored various triazolylidene ruthenium complexes (e.g., **19** and **38**) in olefin metathesis [3, 30]. The complexes were prepared as described in Scheme 6 (Sect. 2.3) starting from robust N1,N3,C4-triarylated or N1, N3-diarylated triazolium salts [2, 63]. The stability of triazolylidene ruthenium complexes to oxidative conditions was of utmost importance to design effective catalysts for olefin metathesis and oxidation reactions. Related complexes with an alkyl substituent at N3 have been noted to be unstable, and, for this reason, polyarylated triazole carbene ligands are strongly preferred.

Complexes **19c** and **19f** were characterized by single-crystal X-ray diffraction and their characteristic bond lengths were very similar to the analogs Grubbs' second-generation imidazole catalyst. For instance, the carbene–Ru bond length (1.99 Å versus 1.98 Å in the imidazole complex), the benzyldiene C–Ru bond length (1.82 Å versus 1.82 Å), and the O–Ru bond length (2.27 Å versus 2.26 Å) were largely conserved across the three species. Notably, the smaller aryl substituent (on C4 in **19c** and N1 in **19f**) is positioned above the Cl–Ru–Cl plane in order to minimize steric interactions with the chloride ligands, while the larger substituent is positioned above the benzyldiene group.

All complexes **19** except **19f** displayed high activity in ring-opening metathesis polymerization (ROMP) of cyclooctadiene (Scheme 25). Kinetic studies indicated that catalyst **19d** performed very efficiently with similar activity to the Grubbs' second-generation catalyst (GII). Ring-closing metathesis (RCM) followed related trends. Complex **19f** was essentially inactive, while complex **19j** performed best and displayed fast initiation as well as catalytic activity similar to GII. Interestingly, metathesis screens revealed that **38** was completely inactive, but acidolysis of the Ru–triazolylidene bond was demonstrated to yield a highly active Ru(NHC) species (see Sect. 3.2), which catalyzed the RCM reaction of test dienes to reach 100% conversion within a few minutes.

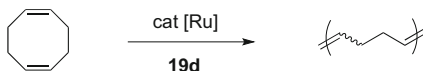
Ruthenium NHC carbene complexes designed to catalyze dehydrogenative oxidation of alcohols and amines have been usefully applied to the preparation of carbonyl compounds, imines, and amides [64, 65]. The new ruthenium(II) triazolylidene complexes **66** and **67** bearing η^6 -arene ligands were prepared by Albrecht [66, 67] according to the established transmetalation and halogen ligand exchange protocols from the corresponding triazolium salt **1d** (Scheme 26).

Both complexes **66** and **67** were checked as catalysts precursors for the dehydrogenative oxidation of alcohols and amines (Scheme 27). Primary and secondary benzylic alcohols were readily oxidized in refluxing toluene with 5 mol% catalyst **66b**, though electron-withdrawing substituents needed longer

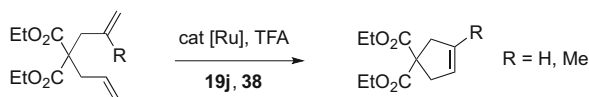


- 19c** ($R^1 = \text{Dipp}$; $R^2 = \text{Ph}$; $R^3 = \text{Dipp}$)
19d ($R^1 = \text{Dipp}$; $R^2 = \text{Mes}$; $R^3 = \text{Dipp}$)
19f ($R^1 = \text{Dipp}$; $R^2 = \text{Tipp}$; $R^3 = \text{Dipp}$)
19j ($R^1 = \text{Mes}$; $R^2 = \text{Ph}$; $R^3 = \text{Mes}$)

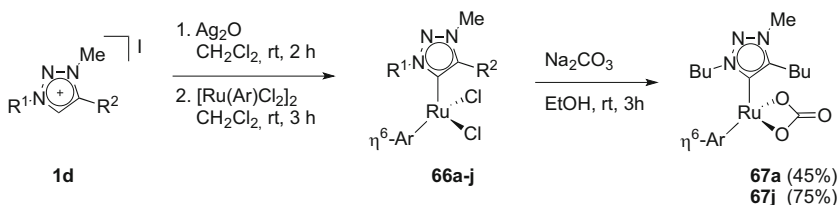
Ring opening metathesis polymerization



Ring closing metathesis



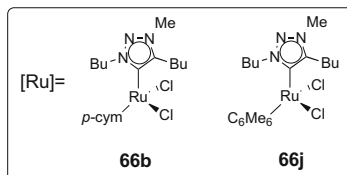
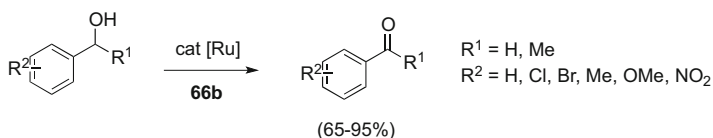
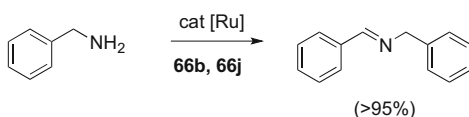
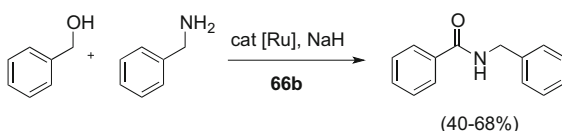
Scheme 25 Ruthenium(II) triazolydene catalysts for olefin metathesis reactions



- | | |
|--|--|
| a ($R^1 = \text{Et}$; $R^2 = \text{Bu}$; $\eta^6\text{-Ar} = p\text{-cym}$) (83%) | f ($R^1 = \text{Bu}$; $R^2 = \text{Ph}$; $\eta^6\text{-Ar} = p\text{-cym}$) (99%) |
| b ($R^1 = \text{Bu}$; $R^2 = \text{Bu}$; $\eta^6\text{-Ar} = p\text{-cym}$) (71%) | g ($R^1 = \text{Bu}$; $R^2 = \text{Mes}$; $\eta^6\text{-Ar} = p\text{-cym}$) (72%) |
| c ($R^1 = \text{Hex}$; $R^2 = \text{Hex}$; $\eta^6\text{-Ar} = p\text{-cym}$) (74%) | h ($R^1 = \text{Mes}$; $R^2 = \text{Ph}$; $\eta^6\text{-Ar} = p\text{-cym}$) (70%) |
| d ($R^1 = \text{Me}$; $R^2 = \text{Ph}$; $\eta^6\text{-Ar} = p\text{-cym}$) (40%) | i ($R^1 = \text{Mes}$; $R^2 = \text{Mes}$; $\eta^6\text{-Ar} = p\text{-cym}$) (77%) |
| e ($R^1 = \text{Et}$; $R^2 = \text{Ph}$; $\eta^6\text{-Ar} = p\text{-cym}$) (85%) | j ($R^1 =$; $R^2 =$; $\eta^6\text{-Ar} = \text{C}_6\text{Me}_6$) (62%) |

Scheme 26 Synthesis of ruthenium(II) η^6 -arene triazolydene complexes

reaction times. Aliphatic alcohols such as 2-phenylethanol and 1-octanol were poor substrates. The oxidation of benzylic amines generated homocoupled imines due to condensation of the initially formed imine with residual amine. Slightly higher reaction temperatures (150°C) were needed than for the analogous alcohol oxidation. When alcohol and amine oxidation were combined, amides were formed in the presence of a base. For instance, reaction of benzyl alcohol with benzylamine in the presence of a catalytic amount of **66b** and NaH afforded the corresponding *N*-benzyl benzamide.

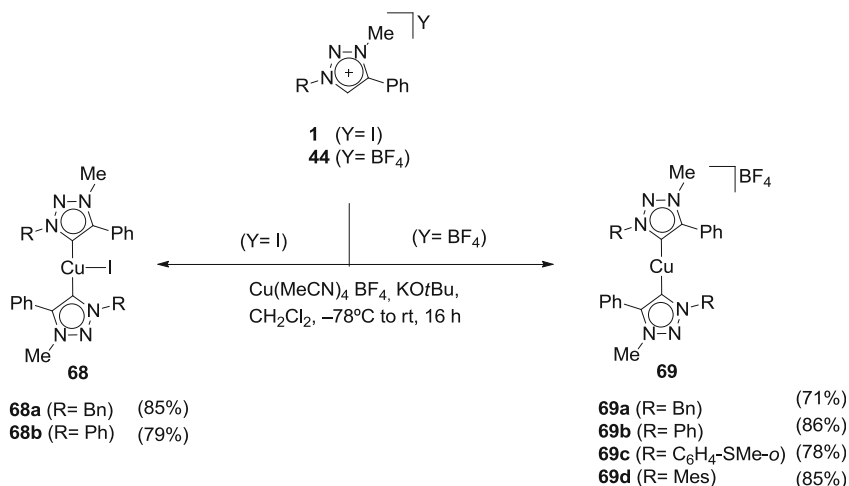
**Alcohol dehydrogenation****Oxidative homocoupling of amines****Amide formation from alcohol and amines**

Scheme 27 Ruthenium(II) η^6 -arene catalysts for dehydrogenative oxidation of alcohols and amines

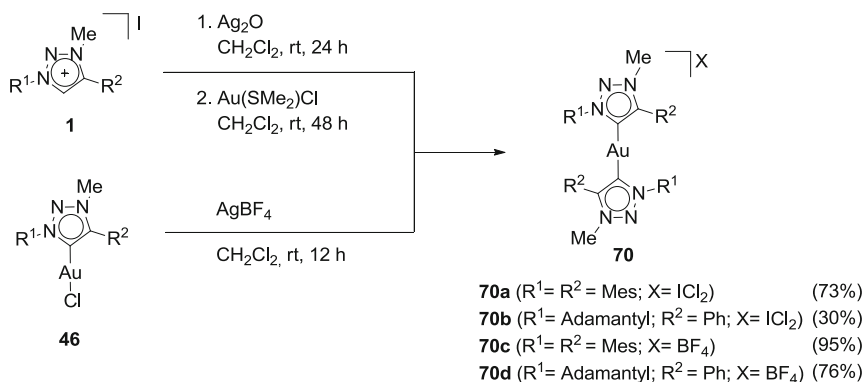
4.2 Dicarbene Complexes (Type B)

4.2.1 Copper

Halide-containing bis(triazolyldiene) copper complexes **68** and halide-free congeners **69** could be selectively synthesized as demonstrated by Sarkar (Scheme 28) [68]. Direct metallation of triazolium iodides **1** with $\text{Cu}(\text{MeCN})_4\text{BF}_4$ in the presence of KO^tBu base afforded the halogenated neutral complexes **68** in excellent yields, whereas tetrafluoroborate salts **44** yielded under the same conditions the cationic compounds **69**. The structures of compounds **68a** and **69d** were unequivocally ascertained by X-ray crystallographic analysis. As expected, cationic complexes **69c–d** catalyzed the CuAAC reaction under low loads (0.5 mol%), proving to be clearly superior to the neutral iodinated complexes **68a–b**.



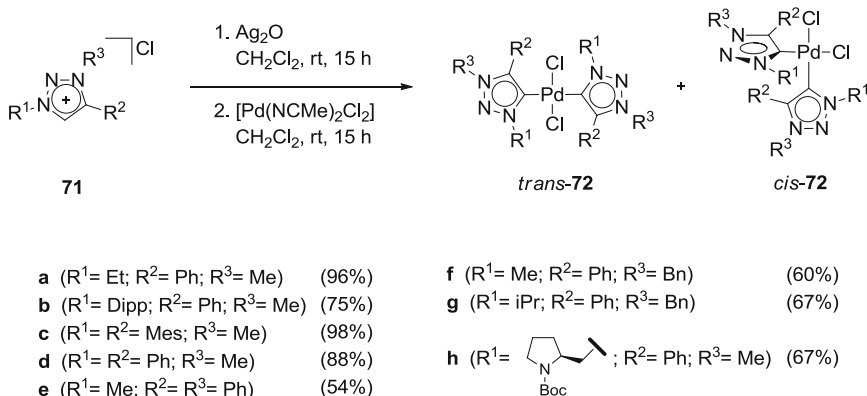
Scheme 28 Synthesis of copper(I) bis(triazolylidene) complexes



Scheme 29 Synthesis of gold(I) bis(triazolylidene) complexes

4.2.2 Gold

Transmetalation of triazolium salts **1** with only 0.5 equiv. of Au(SMe₂)Cl has been demonstrated by Albrecht to provide homoleptic gold(I) biscarbene complexes **70** (Scheme 29) [38]. Alternatively, the same gold complexes were formed by reacting the monodentate complexes **46** with AgBF₄. This procedure afforded the bis(carbene) complexes **70** in higher yields. Silver-assisted formation of complexes **70** from **46** implies a carbene transfer from one Au center to another, indicating that the carbene–Au bond is not very strong in the presence of Ag⁺ ions and that dissociation is facile. The kinetic lability of the carbene ligand in the triazolylidene



Scheme 30 Synthesis of palladium(II) bis(triazolylidene) complexes

gold complexes was further demonstrated by mixing **70c** and the gold complex **46f** (see Scheme 17 in Sect. 4.1). Upon addition of AgBF_4 (10 mol %), formation of the carbene gold complex **46c** was indicated in 40% by NMR analysis, along with the new heteroleptic gold biscarbene complex $[\text{Au}(\text{trzMes}_2)(\text{trzPh}(\text{adam}))]$.

4.2.3 Palladium

Palladium(II) bis(triazolylidene)dichloride complexes **72** can be prepared under appropriate transmetalation conditions without the concomitant formation of dimeric monocarbenes through linear silver biscarbene intermediates (see Sects. 2.1 and 2.2). Starting from diversely substituted chloride triazolium salts **71**, various authors have developed this synthetic route to prepare the mesoionic biscarbene compounds **72** [11, 18, 47, 69–71], including the Sankararaman's first chiral palladium triazolylidene complex **72h** containing a (*S*)-prolinol moiety (Scheme 30) [72]. Mixtures of *cis/trans* isomer complexes **72** were formed depending on the triazole substituents. Isomer proportions could be monitored using NMR spectroscopy by assuming that the *trans* configuration is expected to alleviate steric congestion around the metal coordination sphere and may therefore be more easily accessible than *cis* isomers. Dynamic *cis/trans* isomerization equilibria were often observed upon heating the mixtures of complexes **72**, and, for example, a *cis/trans* isomerization barrier of $\Delta G^\ddagger = 70 \text{ kJ mol}^{-1}$ was calculated for complex **72a** using variable temperature NMR spectroscopy. Sankararaman recently reported on the unexpected stabilization of the *cis*-bis(4-hydroxymethyl-1-phenyl-1,2,3-triazolylidene) palladium dichloride complex taking advantage of the hydrogen bonding of the hydroxyl group and the chloride ligands [73].

Complexes **72** showed the Pd center in a distorted square-planar environment as is typical of such compounds and can be illustrated by the X-ray diffraction

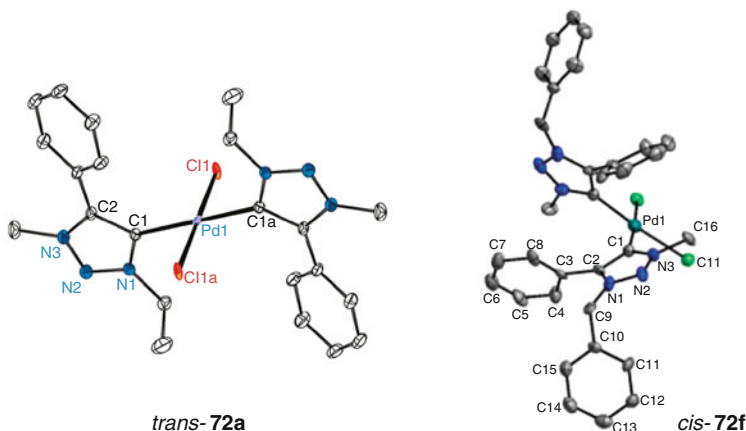
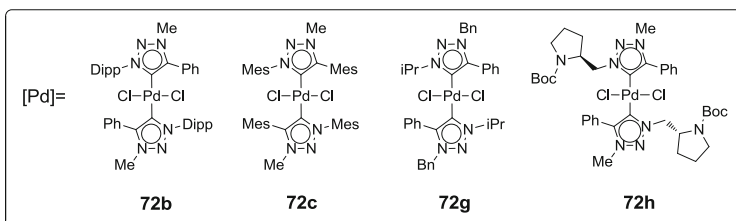
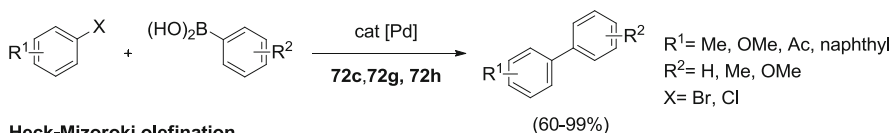
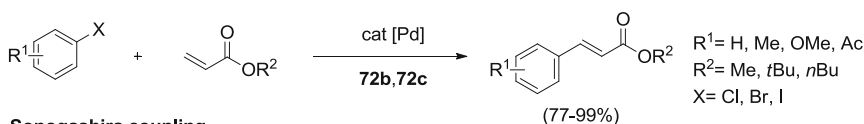
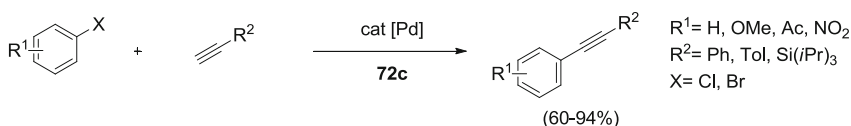


Fig. 7 X-ray structures of palladium(II) bis(triazolylidene) complexes *trans*-**72a** and *cis*-**72f**. Figures partially reprinted from [10] and [70], © 2011 VCH and 2013 RSC

structures of complexes *trans*-**72a** and *cis*-**72f** (Fig. 7). For *trans*-**72a** the Pd–C_{carbene} and Pd–Cl bond lengths were 2.037(3) and 2.3534(8) Å, respectively, and the dihedral angle was 88.8(1), while for *cis*-**72f** the Pd–C_{carbene} and Pd–Cl bond lengths were 1.99(1) and 2.373(3) Å and the angle was 54.0(5).

Palladium(II) biscarbene complexes **72** proved to be very effective for cross-coupling reaction catalysis (Scheme 31). When tested for the Suzuki–Miyaura diarylation reaction, the complexes **72e–g** showed excellent activity with aryl bromide substrates. In each case, yields exceeding 90% were observed within 5 h at room temperature with a catalyst loading of 0.5 mol% in the environmentally benign solvent water. However, with aryl chlorides no product formation was observed under these conditions. Nevertheless, in dry 1,4-dioxane at 120°C and using 1 mol% of the catalyst, yields of about 70% were obtained with **72g** and **72c**. The latter **72c**, which turned out to be the more efficient, catalyzed the Suzuki–Miyaura coupling reaction with aryl and heteroaryl chlorides successfully to give biaryls in excellent yields, particularly for the sterically hindered reaction between *o*-substituted arylchlorides and *o*-substituted phenylboronic acids. Furthermore, it was shown to be very active for multiple Suzuki–Miyaura coupling of polybromoarenes [74].

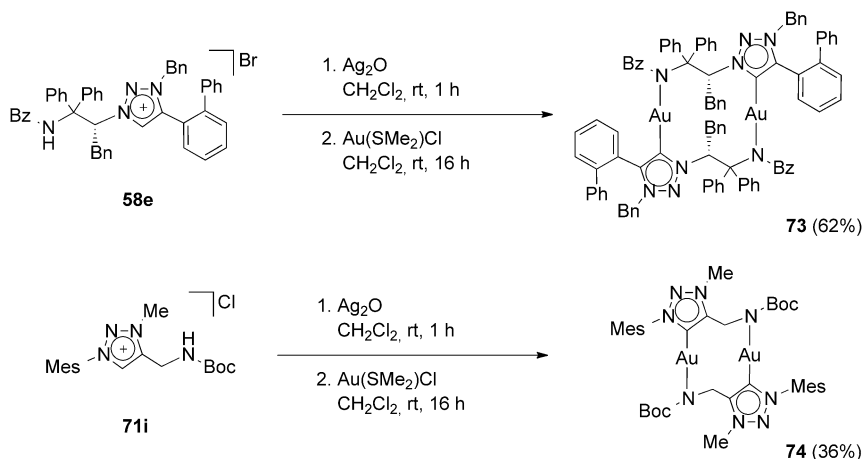
In an attempt to prepare optically active *ortho*-disubstituted biaryl compounds, Sankararaman observed diaryl formation when using the chiral triazolylidene palladium complex **72h** catalyst for the coupling of different aryl bromides with arylboronic acids. At 75°C and with 2–5 mol% **72h**, activated aryl bromides were converted in high yield over several hours. Unfortunately, sterically more demanding substrates, e.g., naphthyl bromides, were poorly converted with phenylboronic acid and were not cross-coupled to naphthylboronic acid, thus preventing the evaluation of a potential asymmetric induction of the chiral ligand **72h**.

**Suzuki-Miyaura coupling****Heck-Mizoroki olefination****Sonogashira coupling**

Scheme 31 Catalytic activity of palladium(II) bis(triazolylidene) complexes in cross-coupling reactions

Fukuzawa and coworkers have described the olefin arylation reaction (Heck–Mizoroki coupling) using **72b–c** as catalysts [75]. The triazolylidene palladium complex **72c** with mesityl wingtip groups induced higher activity than phenyl substituents. Aryl bromides were converted well, but aryl chlorides gave much lower yields and were only converted if activated by an electron-withdrawing group. Heteroatoms and *ortho* substituents constituted a further limitation to this catalyst system. Interestingly, mesoionic complex **72c** was more active than the corresponding 2-imidazolylidene analogs, e.g., $[\text{Pd}(\text{ImMes})_2\text{Cl}_2]$.

Complex **72c** was also effective in the arylation of alkynes (Sonogashira coupling). The reaction was only practical for electron-poor aryl bromides, while electron-donating substituents on the aryl halide induced moderate to low conversion. Conversely, a variety of terminal alkynes were successfully coupled, validating complex **72c** as a catalyst that outperforms the analogous imidazole carbene complex comprising two ImMes ligands. The efficiency of complex **72c** both in the Heck–Mizoroki and the Sonogashira coupling has been exploited to perform tandem reactions. Thus, a sequential Heck-arylation with *tert*-butyl acrylate and



Scheme 32 Synthesis of bidentate dimetallic gold(I) triazolylidene complexes

subsequent Sonogashira coupling of *p*-bromo-iodobenzene with phenylacetylene has been developed to generate the desired product in 69% yield [71].

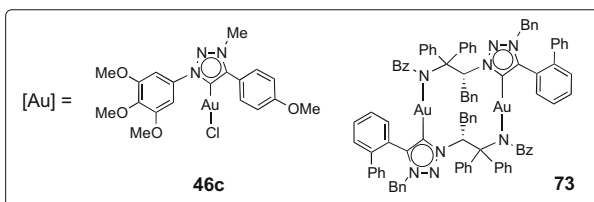
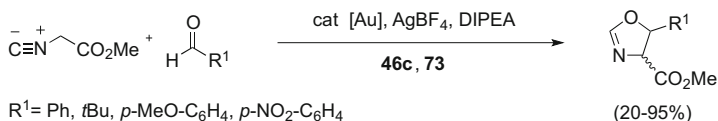
5 Polydentate 1,2,3-Triazolylidene Complexes

5.1 Bidentate Bimetallic Complexes (Type C)

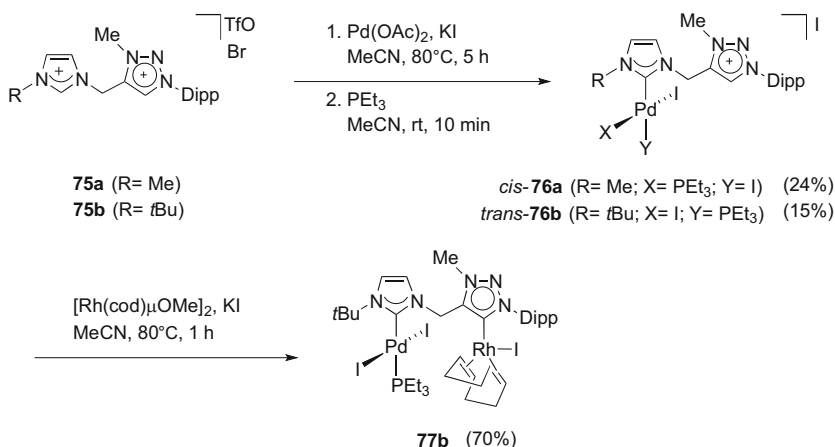
5.1.1 Gold

Amide-functionalized triazolium salts **58e** and **71i** were used by Albrecht to prepare dimetallic gold(I) complexes **73** and **74** bearing bidentate triazolylidene ligands (Scheme 32) [38]. A single-crystal X-ray analysis of complex **74** confirmed the dimeric connectivity pattern.

The monodentate gold complex **46c** (see Scheme 29) and the chiral bidentate complex **73** have been studied as catalysts for the aldol condensation of aldehydes and methyl isocyanoacetate in the presence of AgBF_4 and diisopropylethylamine base (Scheme 33) [38]. With a catalyst load of 1 mol%, benzaldehydes with electron-donating and withdrawing substituents were converted into 1,3-oxazolines as *cis/trans* diastereomeric mixtures ranging from 40/60 to 15/85. Bulky *t*BuCHO was poorly converted, presumably due to steric limitations, but in substantially better *cis/trans* proportion (5/95). Despite the use of the chiral catalyst **73**, no appreciable asymmetric induction was noted for the aldol reaction in any instance.

**Aldol condensation**

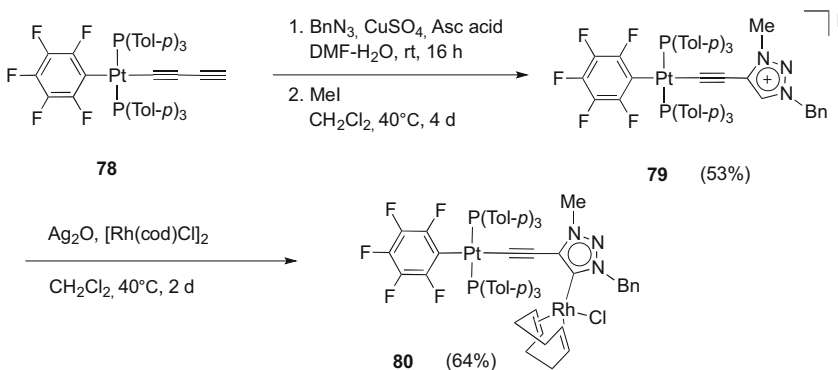
Scheme 33 Gold(I) triazolyldiene catalysts for the aldol condensation of aldehydes and methyl isocyanoacetate



Scheme 34 Synthesis of bidentate mixed dimetallic palladium(II)/rhodium(I) imidazolyldiene/triazolyldiene complexes

5.1.2 Rhodium

Cowie synthesized the first mixed Pd(II)/Rh(I) bimetallic dicarbene complex based on the *N*-heterocyclic/mesoionic carbene framework (Scheme 34) [76]. Following a direct metallation strategy, the dicationic salts **75** were palladated exclusively at the 1,3-imidazole moiety using Pd(OAc)₂ in the presence of potassium iodide. The pendent PdI₃ group of the intermediate imidazolyldiene carbene was further functionalized through iodide substitution with triethylphosphine, which adopted a preferential *cis* or *trans* disposition in the complexes **76**, depending on the bulk of the R group anchored to the imidazole. Finally, a second metallation at the triazole



Scheme 35 Synthesis of a dimetallic platinum(II)/rhodium(I) triazolylidene complex

moiety in *trans*-**76b** using $[\text{Rh}(\text{cod})\mu\text{OMe}]_2$ and KI led to the hybrid complex **77b** in good yield.

In an effort to incorporate a maximum of metal coordination spheres around the triazolylidene moiety, Gladysz has prepared the bimetallic Pt/Rh complex **80** (Scheme 35) [77]. The requisite triazolium salt **79** was prepared by clicking the diyne **78** with benzyl azide, followed by *N*-methylation with methyl iodide. Finally, a one-pot transmetalation reaction with Ag_2O and $[\text{Rh}(\text{cod})\text{Cl}]_2$ yielded the complex **80**.

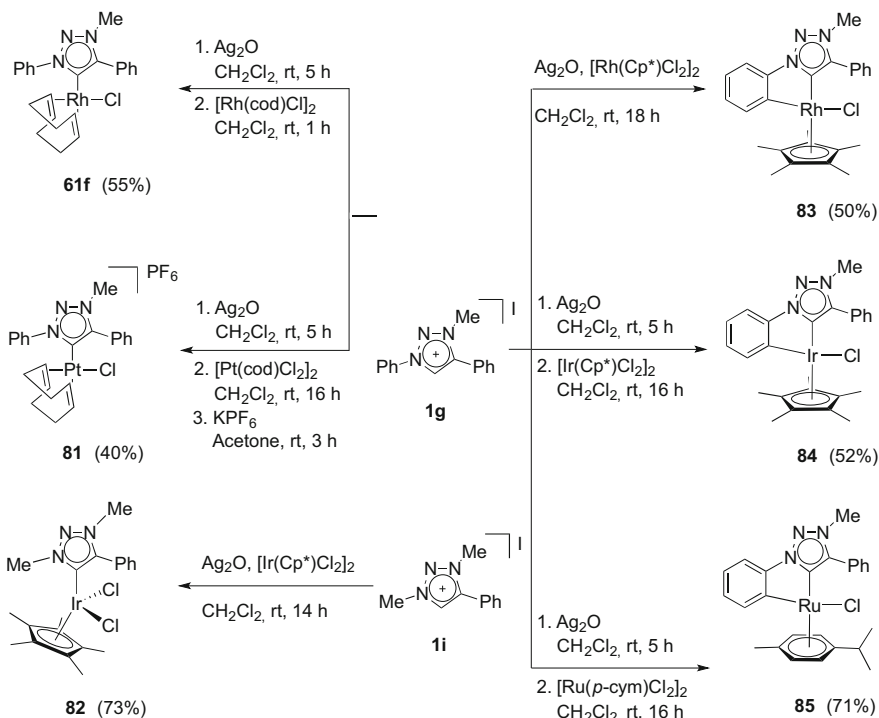
5.2 Cyclometallated Complexes (Type D)

Triazolylidene complexes featuring a metal coordinated to a mesoionic carbene ligand with an additional chelating aryl–metal bond (type D complexes, see Fig. 2) are mostly accessible by cyclometallation reactions as demonstrated by Albrecht [78]. Thus, metallation of 1,4-(di)aryl-substituted triazolium salts (e.g., **1g**) with Ag_2O , followed by transmetalation with electrophilic metal center carriers [e.g., Rh(III), Ir(III), or Ru(II)] usually results in a spontaneous and chemoselective cyclometallation reaction involving C–H bond activation of the *N*-bound aryl group exclusively (cf. **83–85**) (Scheme 36).

The metallacycles in complexes **83–85** were remarkably robust and gave no ring opening upon treatment with HCl in methanol at room temperature during 24 h. Likewise, no deuterium incorporation was detected when complexes **83–85** were treated with $\text{DCl}/i\text{PrOD}-d_8$ at reflux for 10 min. Upon prolonged heating, slow decomposition was noted as the only reactivity pattern. Cyclometallation is substantially easier with electron-rich phenyl rings, e.g., aniline-type arenes that are bound to the N1 nitrogen of the heterocyclic carbene. Less-electrophilic metals such as Rh(I), Ir(I), or Pt(II) yield normal transmetalation complexes (cf. **61f**, **81**),

Less electrophilic metals : Rh(I), Pt(II), Ir(I)

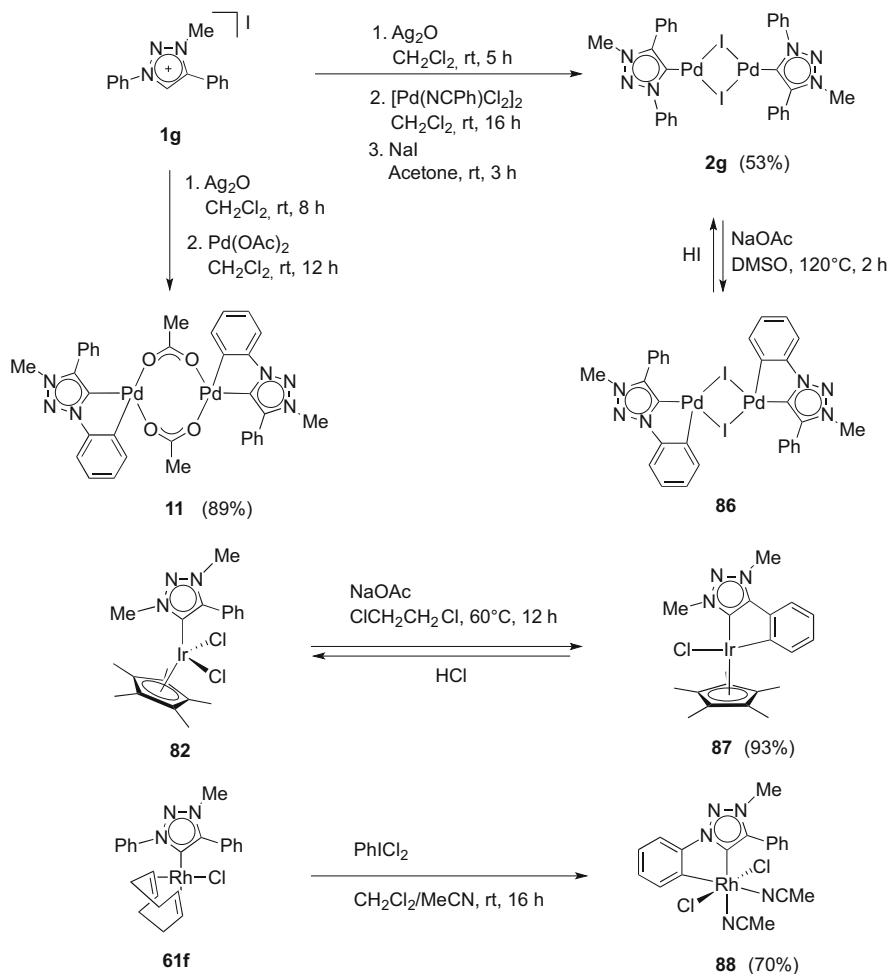
Electrophilic metals : Rh(III), Ir(III), Ru(II)



Scheme 36 Metal electrophilicity and spontaneous cyclometallation of N1-aryl-triazolyli-dene complexes

but not cyclometallation products. Likewise, 4-aryltriazolium salts without *N*-aryl substituents (e.g., the N1, N3-dimethyl salt **1i**) also give monodentate complexes (e.g., **82**), even when strongly electrophilic metals are used [79]. Similarly, triazolium tetrafluoroborates with *ortho*-disubstituted *N*-aryl groups (e.g., 2,6-dimethylphenyl) or with *N*-benzyl groups also failed to give the cyclometallation reaction [80].

Acetate base [81], but not Et_3N , effectively assisted cyclometallation in borderline metal Pd(II) complexes and in activated Ir(III) mesoionic N1, N3-dialkyl complexes (e.g., **82**) with a C-aryl group (Scheme 37). For example, Sankararaman prepared the dinuclear acetate-bridged derivative complex **11** in high yields treating the silver carbene complex generated in situ from the triazolium salt **1g** with Pd (OAc)₂ [18]. In the absence of acetate base, the palladium triazolyli-dene complex **2g** was formed with no cyclopalladation, but, upon addition of sodium acetate, it cleanly underwent cyclopalladation at room temperature to produce complex **86** [11]. In contrast, rhodium complex **61f** and the platinum analog **81** (Scheme 36) were inert to acetate base under a variety of reaction conditions, including the use of AgOAc as a combined proton and halide scavenger.



Scheme 37 Deprotonation- and oxidation-promoted cyclometallation reactions of aryl-triazolylidene complexes

Metallacycle formation is fully reversible. When exposing complex **86** to excess HI, complex **2g** was recovered in high yield. The iridium(III) complexes **82** and **87** behave in a similar way. Complex **82** was converted into a chelate complex **87** increasing pH at moderate temperature and the reaction was reversed treating the cyclometallated complex with anhydrous HCl. Rather than directly forcing a C-H activation, the rhodium(I) complex **61f** was stirred in the presence of dichloro(phenyl)iodine(III), which induced rhodium oxidation and spontaneous cyclometallation to give the rhodium(III) complex **88**. Despite the limited stability of this complex and the formation of detectable amounts of triazolium salt as side

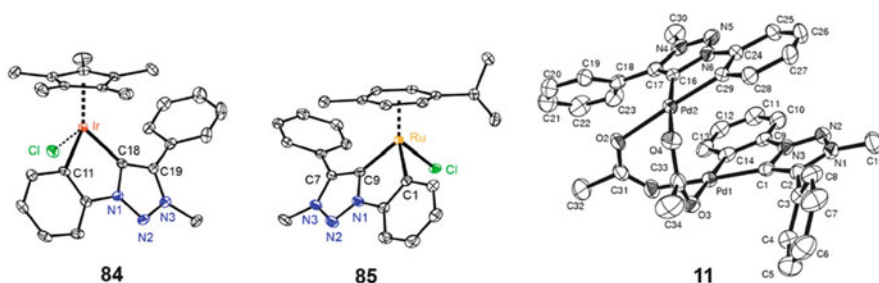


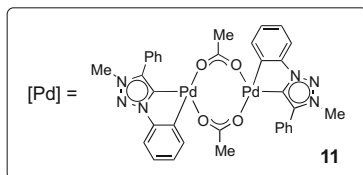
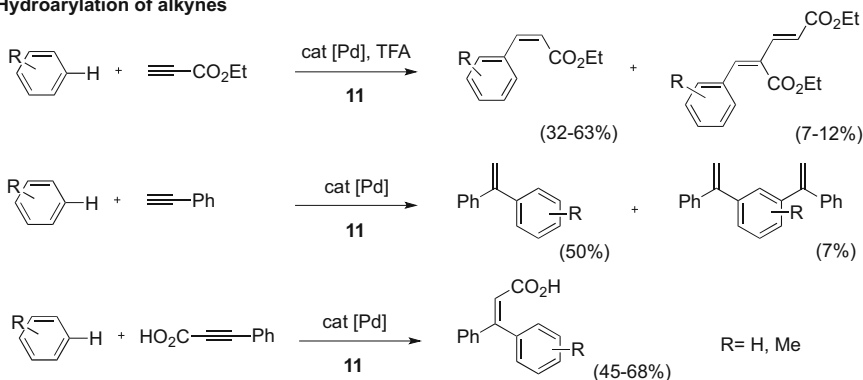
Fig. 8 X-ray diffraction crystal structures of cyclometallated triazolylidene complexes **84**, **85**, and **11**. Figures partially reprinted from [18, 78], © 2011, 2012 ACS

product, unambiguous evidence for the formation of **88** was obtained from NMR spectroscopic analysis. The ^1H NMR spectrum revealed a diagnostic desymmetrization of the N-bound phenyl group into four distinct resonances. Moreover, the phenyl carbon bound to the rhodium center appeared as a doublet at 149.5 ppm ($^1J_{\text{RhC}} = 28.9$ Hz).

X-ray analysis of cyclometallated Ir(III) and Ru(II) complexes **84** and **85** (Fig. 8) showed that metal-triazole carbene bond lengths were not significantly affected by the bidentate bonding mode (2.01–2.03 Å) and the triazolylidene plane coincided with the planar metallacycle. The X-ray structure of the palladium dimeric complex **11** clearly showed a Pd–Pd distance of 2.870 Å, much larger than the Pd–Pd bond distance of 2.56 Å reported earlier for a similar binuclear Pd cyclic complex with acetate bridges [81]. The geometry around each palladium was square planar and the stereochemistry was *cis* with respect to the two triazolylidene and two acetate units. The two tricyclic rings thus formed were within a π -stacking distance of 3.4–3.5 Å. The molecule possessed a C2 axis of symmetry passing through the center of the two palladium atoms.

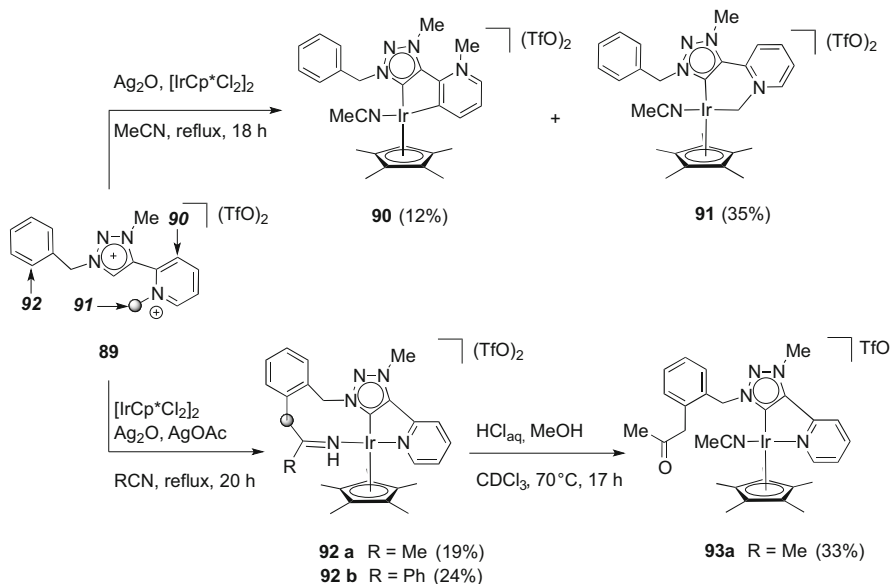
Complex **11** catalyzed the hydroarylation of alkynes, though less efficiently than the normal imidazole Pd analogs (Scheme 38) [82]. For example, reaction of mesitylene with ethyl propiolate produced the corresponding vinylarene stereoselectively, forming only the *Z*-isomer and the double addition product. The reaction worked well for low catalyst loading (0.5%) in the presence of excess TFA in CH_2Cl_2 . In the absence of TFA, only propiolate polymerization took place. Evaluation of the scope of catalyst **11** indicated high activity with electron-rich arenes, while 4-*tert*-butylphenol produced 6-*tert*-butylcoumarin as the single product resulting from an intramolecular transesterification. Phenylacetylene also induced a mixture of mono- and dihydroarylation products. With phenyl propiolic acid, only a single insertion was observed.

Albrecht and coworkers have conducted an elegant study on the cyclometallation of the triazolium salt **89**, bearing a *N*-benzyl group and a *C*-(*N'*-methyl)pyridyl substituent, to put into evidence the selective activation of up to three different C–H bonds depending on the iridium transmetallation reaction

**Hydroarylation of alkynes****Scheme 38** Catalytic activity of palladium(II) dimer complex **11** on the hydroarylation of alkynes

conditions (Scheme 39) [83]. In the absence of acetate base, iridium(III) bidentate complexes **90** and **91** were readily favored from the pyridinium triazolium salt **89** via Ag_2O -mediated proton abstraction and in situ metallation with $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$ in a one-pot procedure. The transformation involved the activation of two C–H bonds in the *N*-methyl pyridine moiety. Complex **90** comprised two different abnormally bound *N*-heterocyclic carbene ligands, that is, a triazolylidene and a 3-pyridylidene, while complex **91** featured a rare ylide bonding mode of the pyridinium ligand precursor, along with the mesoionic triazolylidene.

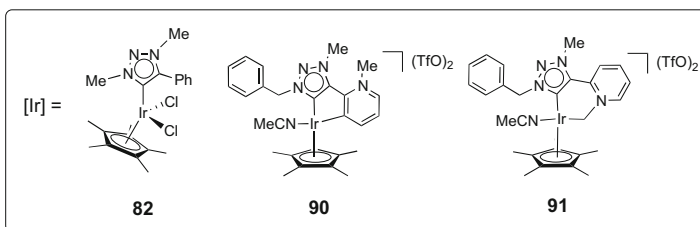
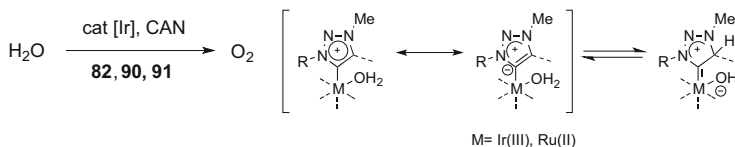
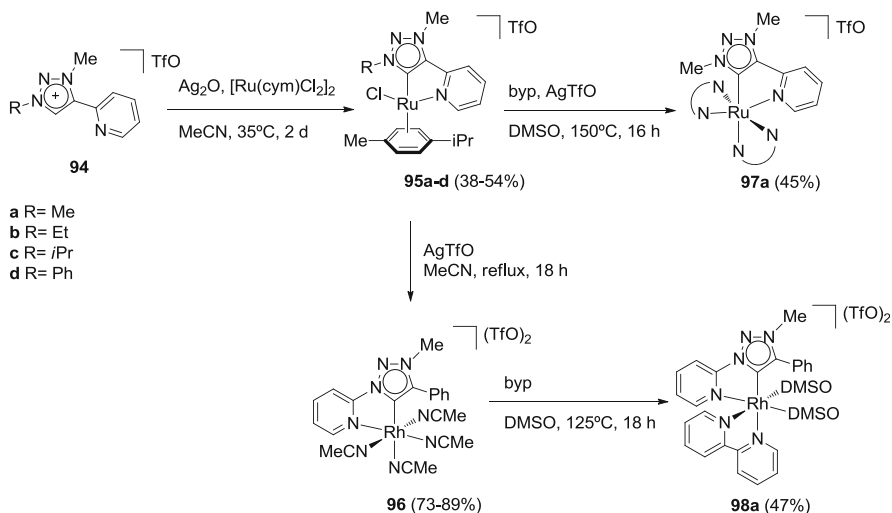
Mechanistic studies supported on the detailed NMR analysis established that complex **90** did not undergo a thermally induced isomerization to yield complex **91** and, hence, the pyridylidene bonding mode in **90** was not an intermediate on the route to the ylide complex **91**. More likely, complexes **90** and **91** shared a common, monodentate triazolylidene iridium intermediate. An unprecedented reactivity was observed when the *N*-benzyl-triazolium salt **89** was metallated with $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$ in the presence of silver acetate. After formation of the triazolylidene–iridium bond, a methylene group was selectively transferred from the pyridinium fragment to the aryl unit of the *N*-bound benzyl group with concomitant activation of a solvent molecule to yield complex **92** comprising a *N,C,N*-tridentate triazolylidene chelate. Formation of **92** involves C–H and C–N bond cleavage and formation of two new $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bonds within the iridium coordination sphere. Isotope labeling experiments unambiguously confirmed the selective transfer of the pyridine-bound carbon. Formally, complex **92a** was the product of a methylene shift from the pyridinium fragment to the benzyl group, and subsequent insertion of a MeCN



Scheme 39 Cyclometallation diversity for iridium(III) *N*-benzyl-*N'*-methyl-pyridyl triazolylidene complex **89**

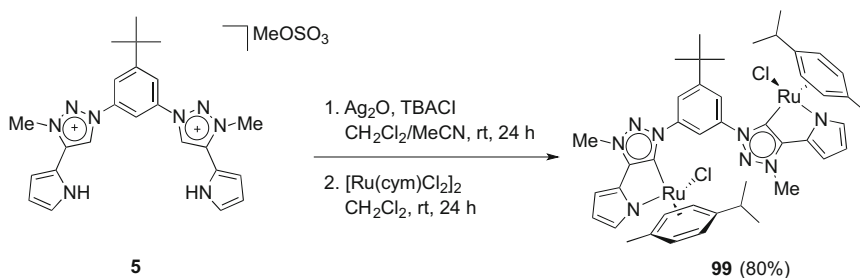
molecule. Support for solvent activation was obtained by carrying out the reaction in benzonitrile (PhCN) instead of MeCN, which yielded complex **92b**.

Owing to the multistep redox processes involved in water oxidation, Albrecht and coworkers considered 1,2,3-triazole carbenes to be advantageous spectator ligands for complexes aimed to catalyze such reaction. Mesoionic carbenes have large contributions from zwitterionic resonance forms, which may assist in stabilizing different metal oxidation states when coordinated to an appropriate transition metal (Scheme 40). In addition, the ligands may serve as a transient reservoir of both positive and negative charge, thus providing synergistic effects similar to those observed in bi- and multimetallic complexes [29, 79]. Iridium(II) complex **82** displays high potential as a water oxidation catalyst. In CAN-mediated oxidation, high turnover numbers were achieved, even though the catalytic performance gradually ceased over extended periods of time (several days). Detailed analysis of the O_2 evolution rate indicated that O_2 production was essentially constant over the first 60 h. The initial turnover frequency (120 h^{-1}) was substantially lower when compared with the activity of chelated species **90**, indicating a beneficial role of the chelate on the catalytic performance. Within 5 days, the TON for complex **90** had nearly reached 10,000, which is the largest number reported to date for water oxidation (TON_{max} for complex **91** is 8350). This productivity corresponds to the formation of almost 1.2 L O_2 per mg of iridium. A detailed study of the evolution of iridium-based catalysis during water oxidation with CAN has been conducted recently by Grotjahn [84].

**Water oxidation****Scheme 40** Water oxidation reaction catalyzed by iridium(III) triazolydene complexes**Scheme 41** Synthesis of ruthenium(II) triazolydene pyridyl complexes**5.3 Chelated Ruthenium Complexes (Type E)**

Llobet and Albrecht have developed a new family of ruthenium-based water oxidation catalysts containing a pyridine-functionalized triazolydene ligand (Scheme 41) [85].

The ruthenium complexes **95** were prepared in moderate yields from the readily accessible pyridine-substituted triazolium salts **94** with Ag_2O and the transmetallating complex $[Ru(cym)Cl_2]_2$. Halide abstraction from **95** with $AgOTf$



Scheme 42 Synthesis of the bidentate ruthenium(II) triazolydene complex **99**

and thermal cymene dissociation in refluxing acetonitrile afforded the dicationic complexes **96** in good yields. Subsequent displacement of the *p*-cymene and chloride ligands in **95** with 2,2-bipyridine (bpy) was accomplished by heating a dimethylsulfoxide (DMSO) solution of the complex in the presence of bpy and AgOTf to afford the highly air- and water-stable complex **97a** [86]. Complex **98a** featuring two solvent ligands was prepared similarly from complex **96a**.

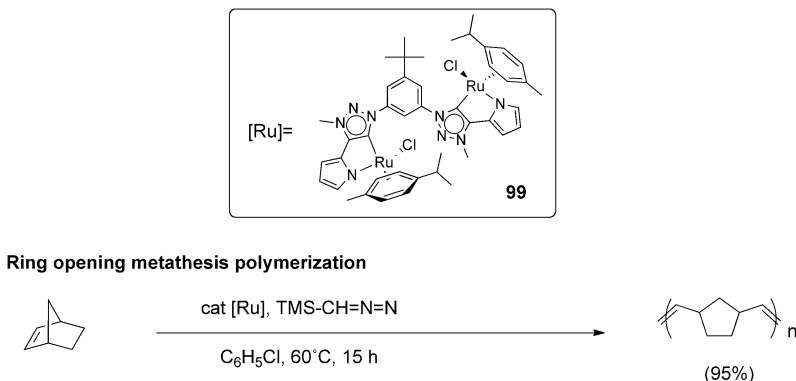
Electrochemical analysis of complexes **95** and **96** revealed a quasireversible oxidation at +1.42 V for complexes **95** and at a slightly lower potential for complexes **96** (+1.35 V). Complex **95d** comprising a withdrawing Ph substituent displayed the highest oxidation potential (1.445 V) and this potential decreased with increasing the donor ability of the substituent R. A different trend was observed in the dicationic complexes **96** with the oxidation potential increasing from Me < *i*Pr < Et << Ph.

Complexes **95** and **96** were all active in the oxidation of water using Ce(IV) as a sacrificial oxidant. The cymene containing complexes **95** generated substantial amounts of CO₂ along with O₂ according to mass spectrometric analysis of the products. The relative CO₂ portion gradually increased over time and was considerably higher with bulkier N-substituents, increasing in the order Me < Et < *i*Pr < Ph. In contrast, the dicationic complexes **96** produced O₂ exclusively.

Bielawski, Sessler, and coworkers [14] have reported the first structurally characterized bis-ruthenium complex **99** supported by a pyrrole-containing bis (1,2,3-triazolydene) ligand identified by an overall 1:2 ligand-to-metal stoichiometry and featuring a discrete ruthenium bimetallic structure (Scheme 42).

The bis(triazolium) salt **5** was subjected to metallation with silver oxide in the presence of tetrabutylammonium chloride and the resulting intermediate silver carbene **6** (see Scheme 3, Sect. 2.1) was reacted with [Ru(*p*-cym)Cl₂]₂ to give the bis-ruthenium(II) complex **99**, containing two triazolydene donor groups in 80% overall yield.

Complex **99** catalyzed the ring-opening metathesis polymerization (ROMP) of norbornene when activated by trimethylsilyldiazomethane, although less strained cyclic olefins such as 1,5-cyclooctadiene or cyclopentene were not efficiently polymerized (Scheme 43). The norbornene polymerization reaction was carried



Scheme 43 Ring-opening metathesis polymerization reaction catalyzed by the ruthenium (II) triazolyldiene complex **99**

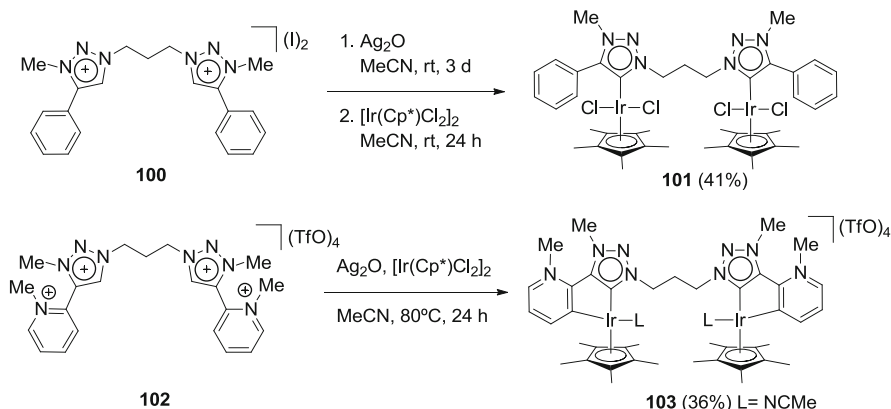
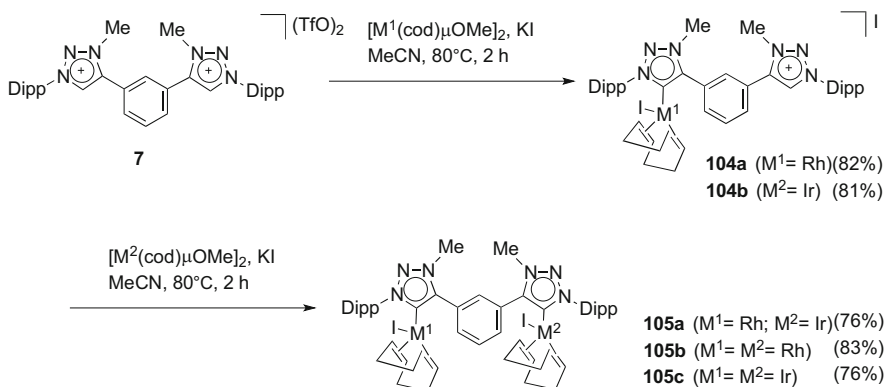
out in chlorobenzene under an atmosphere of nitrogen at 60°C for 15 h with 0.5 mol % of **99** and 3.0 mol% of trimethylsilyldiazomethane (TMSD). Under these conditions, a 95% yield of polynorbornene was obtained.

6 Polydentate Bis(1,2,3-Triazolyldiene) Complexes

6.1 Iridium and Rhodium Complexes (Type F)

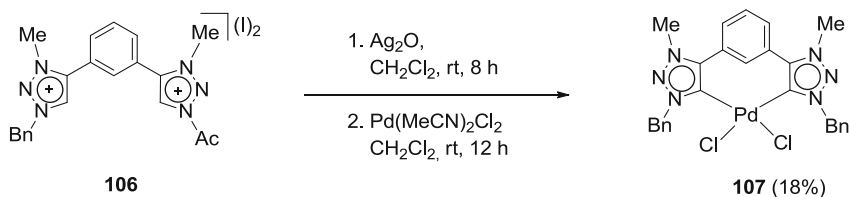
Bimetallic diiridium-triazolyldiene complexes **101** and **103** were investigated by Bernhard and Albrecht to get highly soluble and stable catalysts for water oxidation (Scheme 44) [87]. The reaction of bis(triazolium) salt **100** with Ag_2O for prolonged time at room temperature followed by transmetallation with stoichiometric quantities of $[\text{Ir}(\text{Cp}^*)\text{Cl}_2]_2$ afforded the desired complex **101**. In parallel, the bimetallic chelating complex **103** was synthesized by adding simultaneously Ag_2O and the iridium precursor salt and performing the metallation at 80°C to promote the double cyclometallation of the two pyridine ligands. Both complexes were orange, air-stable compounds that dissolved well in MeCN, water, and MeOH. In contrast to the ionic complex **103**, the neutral diiridium complex **101** was also very soluble in chlorinated solvents. Chelation in **103** was unambiguously deduced from the resonance pattern of the pyridylidene ring, which featured two doublets ($\delta_{\text{H}} = 8.71$ and 8.29 ppm) and a triplet ($\delta_{\text{H}} = 7.60$ ppm), in agreement with the activation of one pyridine C–H bond.

The electrochemical properties of complexes **101** and **103** did not differ significantly from the monometallic model compounds and from related species when evaluated as catalysts for the oxidation of water in the presence of sacrificial CAN.

**Scheme 44** Synthesis of iridium(III) bis(triazolylidene) complexes**Scheme 45** Synthesis of (rhodium(I)/iridium(I) bis(triazolylidene) heterobimetallic complexes 105

However, contrary to the monometallic analogs, the activity was improved when water oxidation was performed under dilute catalyst concentrations.

Cowie has demonstrated that heterobimetallic complex **105a** bridged with a bis(triazolylidene) ligand could be obtained by sequential metallation of the aromatic bistriazolium salt **7** with $[\text{M}(\text{cod})\mu\text{OMe}]_2$ ($\text{M} = \text{Rh}; \text{Ir}$) in the presence of an excess KI to force an iodide product upon metallation (Scheme 45) [88]. Deprotonation of the triazolium moiety was promoted by the basic methoxy ligands of the metallating agents, bypassing the need for the generation of a silver transfer intermediate. The method was suitable only for similarly oxidized metals (e.g., Rh/Ir), but attempts to prepare similar Pd/Rh or Pd/Ir complexes failed.



Scheme 46 Synthesis of the chelated palladium(II) bis(triazolyldiene) complex **107**

6.2 Palladium and Ruthenium Complexes (Type G)

6.2.1 Palladium

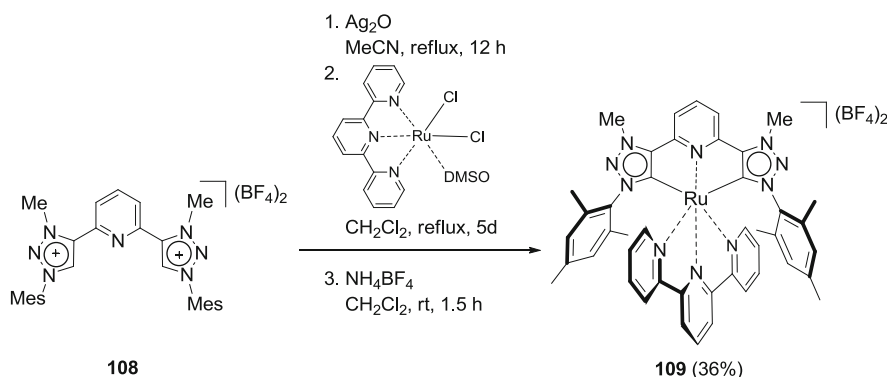
Sankararaman [72] has reported the first example of a pincer palladium complex **107** bearing a MIC ligand based on bis(1,2,3-triazolydene) precursors. Double palladation of **106** was conducted uneventfully following a transmetallation protocol involving treatment with Ag_2O followed by metal exchange with $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ to afford complex **107** in low yield (Scheme 46).

Complex **107** was tested for its catalytic activity in Suzuki coupling. Coupling of 4-bromonitrobenzene and 4-bromobenzonitrile with phenylboronic acid yielded 4-nitro- and 4-cyanobiphenyl, respectively, in >90% yields (see also Sect. 4.2).

6.2.2 Ruthenium

González, Schubert, and coworkers have exploited the superior σ donating of mesoionic carbenes to prepare the heteroleptic ruthenium(II) complex **109** as a promising candidate for photosensitizer applications (Scheme 47) [89]. Complex **109**, comprised of a C,N,C-tridentate coordinating bis(triazolyldiene)-pyridine ligand as a tpy analog (tpy = 2,2',6',2''-terpyridine), was synthesized under mild reaction conditions with a high selectivity and acceptable overall yield. A stable silver(I) carbene was first prepared from the bis(triazolium) tetrafluoroborate **108** by utilizing Ag_2O . For the subsequent transmetallation, ruthenium(II) complex *cis*- $[\text{Ru}(\text{tpy})(\text{DMSO})\text{Cl}_2]$ proved to be a sufficiently selective and reactive precursor to afford the corresponding tpy complex, which was finally treated with excess NH_4BF_4 to exchange the anion affording the dicationic complex **109**.

Luminescence and electrochemical studies conducted by the authors showed that the longest wavelength metal-to-ligand charge transfer MLCT absorption of **109** occurred at the tpy ligand, whereas the triplet metal-centered $^3\text{MLCT}$ emission emerged from the carbene ligand. Increased energy levels of $^3\text{MLCT}$ states due to the strongly donating triazolyldiene ligands in complex **109** efficiently diminished radiationless deactivation, which is an important requisite for photosensitizer applications. Recently, Schubert and Berlinguette have developed a second generation of $\text{Ru}(\text{tpy})\text{bis}(\text{triazolyldiene})$ complexes incorporating terminal carboxylate and



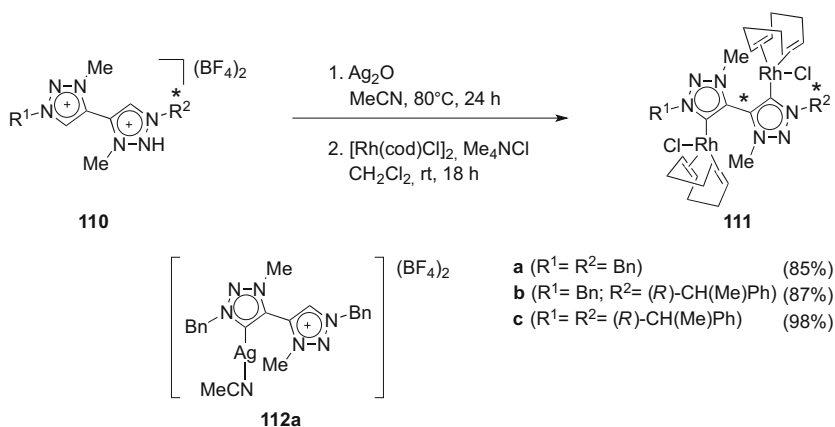
Scheme 47 Synthesis of a chelated ruthenium(II) bis(triazolylidene) complex

phosphonate groups to achieve a robust cooperative anchoring onto TiO_2 surfaces [90, 91].

7 Bidentate 4,4'-Bis(1,2,3-triazolylidene) Complexes

7.1 Rhodium Complexes (Type H)

Aizpurua and coworkers have demonstrated for the first time the potential of 4,4'-bis(1,2,3-triazol)-5,5'-diylidene ligands as atropoisomeric components for the preparation of enantiopure dirhodium(I) complexes **111** featuring configurationally stable axial chirality (Scheme 48) [92]. The method required the use of nonsymmetrically *N*-substituted 4,4'-bis(1,2,3-triazolium) salts **110** as carbene precursors, which were accessible in a totally site-controlled manner by Cu(I)-catalyzed “click” [2+3] cycloaddition of 3-alkyl-4-ethynyl-1,2,3-triazolium salts with alkyl or aryl azides [93]. Submitting the chiral bistriazolium salt **110b** to metallation with Ag_2O under usual room temperature conditions followed by transmetalation with $[\text{Rh}(\text{cod})\text{Cl}]_2$ afforded complex reaction mixtures, whereas carrying the formation of the silver dicarbene in refluxing acetonitrile for 24 h cleanly led to the final dirhodium complex **111b** in high yield. ^1H NMR monitoring evidenced a slow thermodynamic equilibration of the two possible silver dicarbene diastereomers around the C4-C4' biaryl bond to a single complex. Subsequent transmetalation with $[\text{Rh}(\text{cod})\text{Cl}]_2$ to afford the rhodium complexes **111** occurred with total axial configuration integrity and virtually complete diastereomeric excess in each case. The absolute configuration of the newly created C4-C4' chiral axis for the enantiopure atropoisomeric dirhodium complexes **111b-c** was established as (*R*) from the X-ray crystallograms (Fig. 9).



Scheme 48 Synthesis of rhodium(I) 4,4'-bis(triazole)diylidene chiral complexes

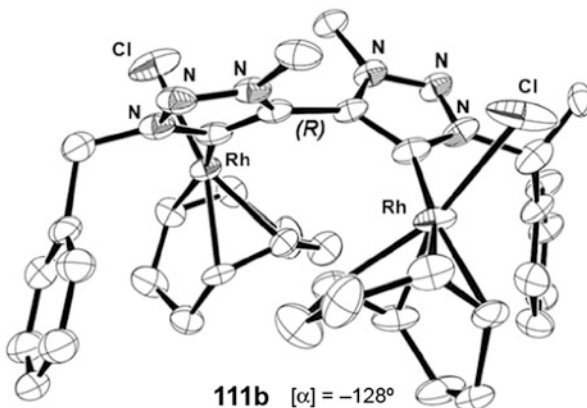
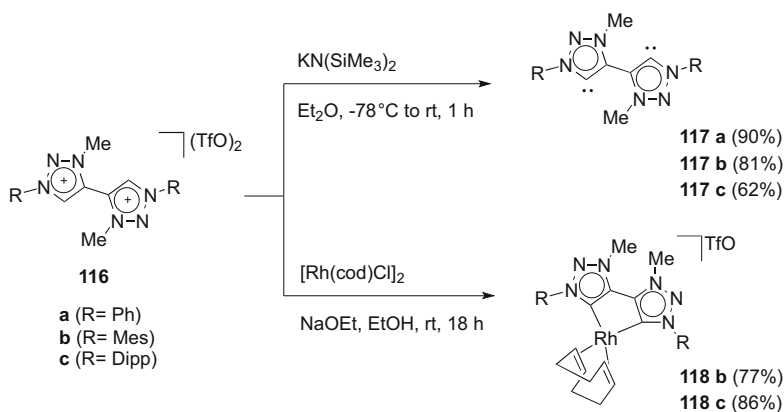


Fig. 9 X-ray structure of the enantiopure rhodium(I) complex **111b**. Figure partially reprinted from [92], © 2012 ACS

A mechanistic study of the formation of silver dicarbene complexes from the bistriazolium salt **110a** allowed for the spectroscopic detection, though no isolation, of the unprecedented monometallated carbene cation complex **112a**. This clearly suggested a strong electronic stabilization of the carbene moiety by the contiguous triazolium cationic ring in **110a** throughout conjugative effects. Cyclic voltammetry analysis of **110a** in the absence of metal cations allowed for the detection of two reduction peaks at -1.6 and -1.3 V assigned to the dicarbene and monocationic carbene species, respectively. Ab initio computational calculations conducted on the model bistriazole structures **113–115** further supported the exceptional stability of mesoionic cation carbenes of the type **114** (Fig. 10).

	113	114	115
HOMO (eV)	-4.11	-8.30	-4.51
HOMO/LUMO gap (Kcal·mol ⁻¹)	54.5	42.4	57.3
Proton affinity PA ₁ (Kcal·mol ⁻¹)	280.0	181.1	269.7

Fig. 10 Stabilization of cation carbene **114** by conjugative effects estimated by ab initio calculations (Gaussian09; BP86/def2-SVP)



Scheme 49 Synthesis of chelated rhodium(I) 4,4'-bis(triazolylidene) complexes

7.2 Rhodium Complexes (Type I)

Following the free carbene isolation strategy, Bertrand has reported the first preparation of a metal-free mesoionic dicarbene and has demonstrated its incorporation as a bidentate chelating ligand into rhodium(I) complexes (Scheme 49) [94]. Accordingly, deprotonation of triazolium salts **116** with KHMDS in diethyl ether or tetrahydrofuran at -78°C allowed for the isolation of the free species **117** in good to excellent yields. Alternatively, the direct metallation of bis(triazolium) salts **116b–f** with the basic ligand bearing rhodium dimer complex $[\text{Rh}(\text{cod})(\text{OEt})_2]$ afforded the chelated complexes **118b–c** in 77–86% yield.

The X-ray structure of the free dicarbene **117a** featured two triazolylidene rings adopting antiperiplanar geometry with a torsion angle (C1–C2–C3–C4) of 166.1° (Fig. 11).

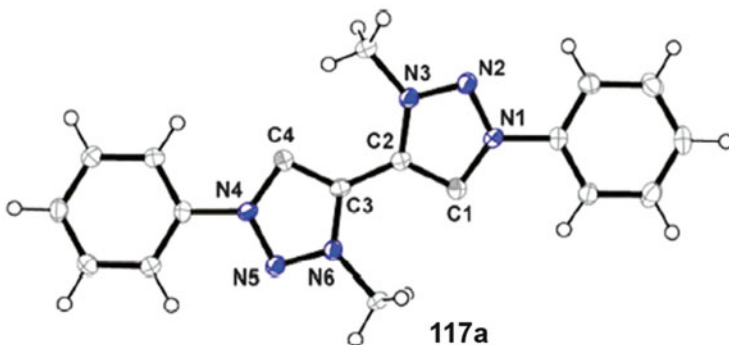


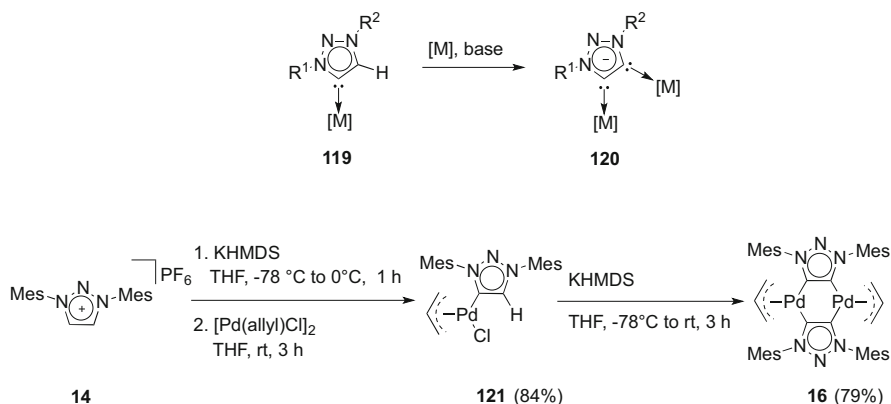
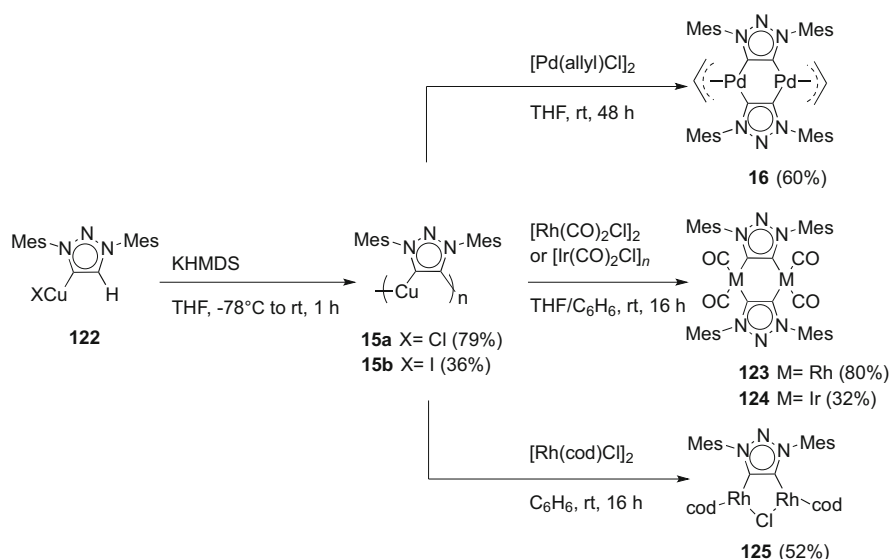
Fig. 11 Crystal structure of the free 4,4'-bis(1,2,3-triazol-5-ylidene) dicarbene **117a**. Figure partially reprinted from [94], © 2011 ACS

8 Bridged 1,2,3-Triazol-4,5-diylidene Complexes (Type J)

Inspired by the preparative method of pyrazolate complexes [95], Bertrand and coworkers have envisioned that deprotonation of the 4-position of triazolylidene-transition-metal complexes **119**, followed by metal coordination, would give anionic 1,2-dicarbene dimetalic 1,2-dihapto complexes **120** [20]. To implement this idea, the starting triazolium salt **14** was deprotonated by KHMDS followed by direct palladation to yield the mesoionic triazolylidene allylpalladium complex **121**, which was treated with KHMDS again to afford exclusively the bridged palladium complex **16** (Scheme 50).

The ^{13}C NMR spectrum of **16** showed only one set of mesityl signals and a single carbene peak at $\delta = 169.5$ ppm. An X-ray diffraction study demonstrated that **16** was a dimetallic complex and adopted a boat conformation. The Pd–C_{allyl} bond lengths [2.005(11)–2.061(11) Å] were significantly longer than that in pyrazolate allylpalladium complexes [2.10–2.13 Å], indicating the stronger electron-donating capabilities of the anionic dicarbene.

The same sequential synthetic route was applied to copper complexes **15** (Scheme 51), which were obtained as oligomeric or polymeric complexes. When **15** was treated with dimeric allylpalladium chloride or $[\text{M}(\text{CO})_2\text{Cl}]_2$ (M = Rh, Ir), bridged bistriazolic complexes **16**, **123**, and **124** were formed. Conversely, treatment of copper complex **15** with $[\text{Rh}(\text{cod})\text{Cl}]_2$ at room temperature gave **125**. The ^1H NMR showed the cyclooctadiene and the MIC in a 2:1 ratio, indicating that **125** was not a dimeric complex, but was comprised of two metal centers coordinated to a single triazole-diylidene ligand. A single-crystal X-ray diffraction study demonstrated that the two rhodium atoms were bridged by a chloride and a triazole dicarbene to form a five-membered $\text{Rh}_2\text{C}_2\text{Cl}$ ring, which adopted an envelope conformation with a short Rh–Rh distance (3.226 Å) (Fig. 12).

**Scheme 50** Synthetic route to anionic 1,2-dicarbene complexes**Scheme 51** Synthesis of bridged dimetallic complexes by copper carbene transmetalation

9 Conclusions and Outlook

The chemistry of mesoionic 1,2,3-triazole-based carbenes has experienced a remarkable and fast growth since the first report of a stable transition metal complex with a triazolylidene ligand in 2008. Mirroring the abundant prior information available for imidazole NHCs [96], and taking advantage of the efficiency and simplicity of the copper-catalyzed azide-alkyne “click” chemistry to prepare the

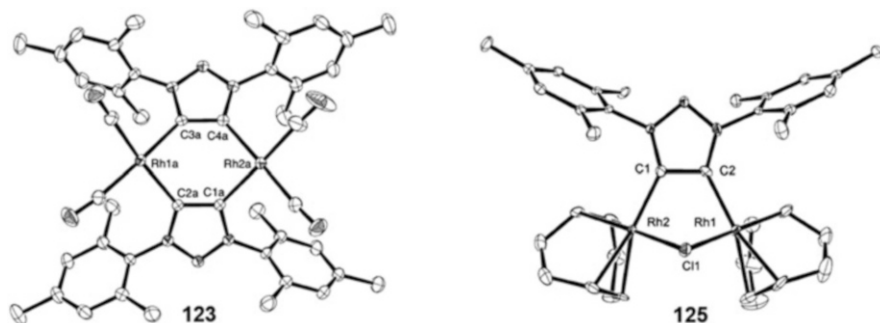


Fig. 12 Crystal structures of the rhodium(I) complexes **123** and **125**. Figures partially reprinted from [20], © 2012 VCH

1,2,3-triazole ligand precursors, a systematic quest for novel triazolylidene structures and metal complexes thereof has been launched in recent years. By far, the triazolium ion/silver carbene/transmetallation route has demonstrated to be the method of choice to synthesize a large variety of triazolylidene carbene complexes, encompassing monodentate, polydentate, chelated, and bridged ligands. On the other hand, organometallic catalysis has been the favorite field of application for most novel mesoionic carbene complexes, together with the technologically appealing catalytic water oxidation for energy storage purposes and photosensitizer development for advanced photovoltaic applications.

Mesoionic carbene complexes incorporating task-specific or chiral wingtips to their triazole core will represent an exciting new frontier in the realm of organometallic compounds that hold promise as catalysts for asymmetric synthesis. In addition, recent developments of 1,2,3-triazolium-containing ionic liquids and polymer materials [97] open the way to immobilized catalysts containing such mesoionic metal complexes. In coming years, a subtle balance in complexity, specificity, and robustness in novel mesoionic triazoles should allow these compounds to reach their maturity not only in the field of organometallic chemistry but also in catalysis, material science, or bioinorganic chemistry.

References

1. Arduengo AJ III, Harlow RL, Kline M (1991) *J Am Chem Soc* 113:361
2. Guisado-Barrios G, Bouffard J, Donnadieu B, Bertrand G (2010) *Angew Chem Int Ed* 49:4759
3. Bouffard J, Keitz BK, Tonner R, Guisado-Barrios G, Frenking G, Grubbs RH, Bertrand G (2011) *Organometallics* 30:2617
4. Crudden CM, Allen DP (2004) *Coord Chem Rev* 248:2247
5. Arnold PL, Pearson S (2007) *Coord Chem Rev* 251:596
6. Albrecht M (2009) *Chimia* 63:105
7. Donnelly KF, Petronilho A, Albrecht M (2013) *Chem Commun* 49:1145

8. Crabtree RH (2013) *Coord Chem Rev* 257:755
9. Mathew P, Neels A, Albrecht M (2008) *J Am Chem Soc* 130:13534
10. Schuster EM, Botoshansky M, Gandelman M (2011) *Dalton Trans* 40:8764
11. Poulain A, Canseco-Gonzalez D, Hynes-Roche R, Müller-Bunz H, Schuster O, Stoeckli-Evans H, Neels A, Albrecht M (2011) *Organometallics* 30:1021
12. Baker MV, Brown DH, Simpson PV, Skelton BW, White AH (2009) *Eur J Inorg Chem* 1977
13. Lin IJB, Vasam CS (2007) *Coord Chem Rev* 251:642
14. Cai J, Yang X, Arumugam K, Bielawski CW, Sessler JL (2011) *Organometallics* 30:5033
15. Keske EC, Zenkina OV, Wang R, Crudden CM (2012) *Organometallics* 31:456
16. Canseco-Gonzalez D, Gniewek A, Szulmanowicz M, Müller-Bunz H, Trzeciak AM, Albrecht M (2012) *Chem Eur J* 18:6055
17. Teraasima T, Inomata S, Ogata K, Fukuzawa S (2012) *Eur J Inorg Chem* 1387
18. Saravanakumar R, Rankumar V, Sankararaman S (2011) *Organometallics* 30:1689
19. Lin JCY, Huang RTW, Lee CS, Bhattacharyya A, Hwang WS, Lin IJB (2009) *Chem Rev* 109:3561
20. Yan X, Bouffard J, Guisado-Barrios G, Donnadieu B, Bertrand G (2012) *Chem Eur J* 18:14627
21. Hohloch S, Su C, Sarkar B (2011) *Eur J Inorg Chem* 3067
22. Schaper L, Öfele K, Kadyrov R, Bechlars B, Drees M, Cokoja M, Herrmann WA, Kühn FE (2012) *Chem Commun* 48:3857
23. Nolte C, Mayer P, Straub BF (2007) *Angew Chem Int Ed* 46:2101
24. Partyka DV, Gao L, Teets TS, Updegraff JB, Deligonul N, Gray TG (2009) *Organometallics* 28:6171
25. Álvarez CM, García-Escudero LA, García-Rodríguez R, Miguel D (2012) *Chem Commun* 48:7209
26. Schuster EM, Botoshansky M, Gandelman M (2008) *Angew Chem Int Ed* 47:4555
27. Schuster EM, Botoshansky M, Gandelman M (2009) *Organometallics* 28:7001
28. Schuster EM, Nisnevish G, Botoshansky M, Gandelman M (2009) *Organometallics* 28:5025
29. Lalrempuia R, McDaniel ND, Müller-Bunz H, Bernhard S, Albrecht M (2010) *Angew Chem Int Ed* 49–9765
30. Keitz BK, Bouffard J, Bertrand G, Grubbs RH (2011) *J Am Chem Soc* 133:8498
31. Petronilho A, Müller-Bunz H, Albrecht M (2012) *Chem Commun* 48:6499
32. Nakamura T, Terashima T, Ogata K, Fukuzawa S-I (2011) *Org Lett* 13:620
33. Inomata H, Ogata K, Fukuzawa S-I, Hou Z (2012) *Org Lett* 14:3986
34. Mankad NP, Gray TG, Laitar DS, Sadighi JP (2004) *Organometallics* 23:1191
35. Hohloch S, Sarkar B, Nauton L, Cisnetti F, Gautier A (2013) *Tetrahedron Lett* 54:1808
36. Inomata H, Toh A, Mitsui T, Fukuzawa S-I (2013) *Tetrahedron Lett* 54:4729
37. Kilpin KJ, Paul USD, Lee A, Crowley JD (2011) *Chem Commun* 47:328
38. Canseco-González D, Petronilho A, Müller-Bunz H, Ohmatsu K, Ooi T, Albrecht M (2013) *J Am Chem Soc* 135:13193
39. Dash C, Shaikh MM, Butcher RJ, Ghosh P (2010) *Inorg Chem* 49:4972
40. De Fremont P, Scott NM, Stevens ED, Nolan SP (2005) *Organometallics* 24:2411
41. De Fremont P, Marion N, Nolan SP (2009) *Organomet. Chem* 694:551
42. Chiou JYZ, Luo SC, You WC, Bhattacharyya A, Vasam CS, Huang CH, Lin IJB (2009) *Eur J Inorg Chem* 1950
43. Schaper L-A, Wei X, Hock SJ, Pöthig A, Öfele K, Cokoja M, Herrmann WA, Kühn E (2013) *Organometallics* 32:3376
44. Scherbaum F, Grohmann A, Huber B, Kriger C, Schmidbaur H (1988) *Angew Chem Int Ed Engl* 27:1544
45. de Frémont P, Scott NM, Stevens ED, Nolan SP (2005) *Organometallics* 24:2411
46. Terashima T, Inomata S, Ogata K, Fukuzawa S (2012) *Eur J Inorg Chem* 1387
47. Keske EC, Zenkina OV, Wang R, Crudden CM (2012) *Organometallics* 31:6215
48. Heckenroth M, Kluser E, Neels A, Albrecht M (2007) *Angew Chem Int Ed* 46:6293

49. Heckenroth M, Neels A, Garnier MG, Aebi P, Ehlers AW, Albrecht M (2009) *Chem Eur J* 15:9375
50. Huang J, Hong J-T, Hong S H (2012) *Eur J Org Chem* 6630
51. Huynh HV, Jotsibas R, Yang JA (2009) *Organometallics* 28:5395
52. Han Y, Huynh HV, Tan GK (2007) *Organometallics* 26:6447
53. Chernyshova ES, Goddard R, Pörschke K-R (2007) *Organometallics* 26:3236
54. Baker MV, Barnard PJ, Brayshaw SK, Hickey JL, Skelton BW, White AH (2005) *Dalton Trans* 37
55. Herrmann WA, Runte O, Artus GJ (1995) *Organomet Chem* 501:C1
56. Cetinkaya B, Dixneuf P, Lappert MFJ (1974) *Chem Soc Dalton Trans* 1827
57. Herrmann WA, Elison M, Fischer J, Köcher C, Artus GRJ (1996) *Chem Eur J* 2:772
58. Kelly RA, Clavier H, Guidice S, Scott NM, Stevens ED, Bordner J, Samardjiev I, Hoff CD, Cavallo L, Nolan SP (2008) *Organometallics* 27:202
59. Wolf S, Plenio HJ (2009) *Organomet Chem* 694:1487
60. Fürstner A, Alcarazo M, Krause H, Lehmann CW (2007) *J Am Chem Soc* 129:12676
61. Song G, Zhang Y, Li X (2008) *Organometallics* 27:1936
62. Kuchenbeiser G, Soleilhavoup M, Donnadieu B, Bertrand G (2009) *Chem Asian J* 4:1745
63. Weng M, Geyer A, Friemel A, Jochims JC, Lutz M (2000) *J Prakt Chem* 342:486
64. Shvo Y, Czarkie D, Rahamim Y, Chodosh DF (1986) *J Am Chem Soc* 108:7400
65. Hollmann D, Bahn S, Tillack A, Beller M (2007) *Angew Chem Int Ed* 46:8291
66. Canseco-Gonzalez D, Albrecht M (2013) *Dalton Trans* 42:7424
67. Prades A, Peris E, Albrecht M (2011) *Organometallics* 30:1162
68. Hohloch S, Scheiffele D, Sarkar B (2013) *Eur J Inorg Chem* 3956
69. Nakamura T, Ogata K, Fukuzawa S (2010) *Chem Lett* 39:920
70. Hohloch S, Frey W, Su C-Y, Sarkar B (2013) *Dalton Trans* 42:11355
71. Inomata S, Hiroki H, Terashima T, Ogata K, Fukuzawa S-I (2011) *Tetrahedron* 67:7263
72. Karthikeyan T, Sankararaman S (2009) *Tetrahedron Lett* 50:5834
73. Saravanakumar R, Ramkumar V, Sankararaman S (2013) *J Organomet Chem* 736:36
74. Shaik JB, Ramkumar V, Varghese B, Sankararaman S (2013) *Beilstein J Org Chem* 9:698
75. Kantchev EAB, O'Brien CJ, Organ MG (2007) *Angew Chem Int Ed* 46:2768
76. Zamora MT, Ferguson MJ, McDonald R, Cowie M (2012) *Organometallics* 31:5463
77. Clough MC, Zeits PD, Bhuvanesh N, Gladysz J (2012) *Organometallics* 31:5231
78. Donnelly KF, Lalrempuia R, Müller-Bunz H, Albrecht M (2012) *Organometallics* 31:8414
79. Petronilho A, Rahman M, Woods JA, Al-Sayyed H, Müller-Bunz H, MacElroy D, Bernhard S, Albrecht M (2012) *Dalton Trans* 41:13074
80. Ogata K, Inomata S, Fukuzawa S-I (2013) *Dalton Trans* 42:2362
81. Powers D, Benitez D, Tkatchouk E, Goddard WA, Ritter T (2010) *J Am Chem Soc* 132:14092
82. Viciu M, Stevens ED, Petersen JL, Nolan SP (2004) *Organometallics* 23:3752
83. Lalrempuia R, Müller-Bunz H, Albrecht M (2011) *Angew Chem Int Ed* 50:9969
84. Grotjahn DB, Brown DB, Martin JK, Marelius DC, Abadjian MC, Tran HN, Kalyuzhny G, Vecchio KS, Specht ZG, Cortes-Llanas SA, Miranda-Soto V, van Niekerk C, Moore CE, Rheingold AL (2011) *J Am Chem Soc* 133:19024
85. Bernet L, Lalrempuia R, Ghattas W, Mueller-Bunz H, Vigara L, Llobet A, Albrecht M (2011) *Chem Commun* 47:8058
86. Leigh V, Ghattas W, Lalrempuia R, Müller-Bunz H, Pryce MT, Albrecht M (2013) *Inorg Chem* 52:5395
87. Petronilho A, Woods J A, Bernhard S, Albrecht M (2014) *Eur J Inorg Chem* 708
88. Zamora M, Ferguson MJ, Cowie M (2012) *Organometallics* 31:5384
89. Schulze B, Escudero D, Friebe C, Siebert R, Görls H, Köhn U, Altuntas E, Baumgaertel A, Hager MD, Winter A, Dietzek B, Popp J, Gonzalez L, Schubert US (2011) *Chem Eur J* 17:5494
90. Brown DG, Sanguabtrakun N, Schulze B, Schubert US, Berlinguette CP (2012) *J Am Chem Soc* 134:12354

91. Brown DG, Schauer PA, Borau-Garcia J, Fancy BR, Berlinguette CP (2013) *J Am Chem Soc* 135:1692
92. Aizpurua JM, Sagartzazu-Aizpurua M, Monasterio Z, Azcune I, Mendicute C, Miranda JI, García-Lecina E, Altube A, Fratila RM (2012) *Org Lett* 14:1866
93. Aizpurua JM, Sagartzazu-Aizpurua M, Azcune I, Miranda JI, Monasterio Z, García-Lecina E, Fratila RM (2011) *Synthesis* 17:2737
94. Guisado-Barrios G, Bouffard J, Donnadiou B, Bertrand G (2011) *Organometallics* 30:6017
95. Zhang J-P, Zhang Y-B, Lin J-B, Chen X-M (2012) *Chem Rev* 112:1001
96. Schuster O, Yang L, Raubenheimer HG, Albrecht M (2009) *Chem Rev* 109:3445
97. Aizpurua JM, Fratila RM, Monasterio Z, Perez-Esnaola N, Andreieff E, Irastorza A, Sagartzazu-Aizpurua M (2014) *New J Chem.* 38:474
98. Liebscher J, Jacob Z (2014) 1,2,3-triazolium ionic liquids. *Top Heterocycl Chem*

Top Heterocycl Chem (2015) 40: 269–324

DOI: 10.1007/7081_2014_122

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Published online: 26 March 2014

Multicomponent and Domino Reactions Leading to 1,2,3-Triazoles

N.T. Pokhodylo

Abstract In most cases, application of multicomponent and domino reactions in organic synthesis allows solving complex problems in a simple synthetic way, involving the saving of materials, ensuring of a safe work environment, and the abatement of the number of processes and manipulations performed. In general, these processes are more environmentally friendly and economically profitable. The usage of such reactions in triazole chemistry, which is directly linked with the work with dangerous, explosive, and toxic reagents, facilitates the obtaining of derivatives with valuable properties and opens new opportunities to their widespread application for medical and industrial purposes. This review highlights the key strategies and tactical approaches for the use of multicomponent and domino reactions in the recent reports that clearly demonstrate the advantages of their application in molecular design of the triazole derivatives.

Keywords 1,2,3-Triazoles · Alkynes · Azides · Condensation · Cycloadditions · Domino reactions · Multicomponent reactions

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Abbreviations

aq.	Aqua
AAC	Azide-alkyne cycloaddition
AIL	Amino acid ionic liquids
Ac	Acetyl
Ar	Aryl
Bn	Benzyl
BMIM	1-Butyl-3-methylimidazolium
Boc	Tert-butoxycarbonyl
Bt	Benzotriazole
BTC	Benzene-1,3,5-tricarboxylate
CAN	Ceric ammonium nitrate
Cp	1,2,3,4,5-Pentamethylcyclopentadiene
CuAAC	Copper(I)-catalyzed azide-alkyne cycloaddition
dppf	1,1-Bis(diphenylphosphanyl)ferrocene
DCM	Dichloromethane
DFT	Density functional theory
DIPEA	<i>N,N</i> -Diisopropylethylamine
DMAP	<i>N,N</i> -dimethyl-4-aminopyridine
DMEDA	<i>N,N'</i> -dimethyl-1,2-ethylenediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulphoxide
DTBB	4,4'-Di-tert-butylbiphenyl
ee	Enantiomer excess
eq.	Equivalent(s)
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide

Gly	Glycine
His	Histidine
Hmim	1-Methyl-1 <i>H</i> -imidazolium
HTIB	[Hydroxy(tosyloxy)iodo]benzene
IAAC	Intramolecular Azide-alkyne cycloaddition
MAO	Methylaluminoxane
MAP	Mitogen-activated protein kinases
MCM	Mobil Composition of Matter
MeCN	Acetonitrile
MCR	Multicomponent reaction
MW	Microwave
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
Nf	Nonafluorobutanesulphonyl
NHC	<i>N</i> -heterocyclic carbene
NIS	<i>N</i> -iodosuccinimide
Orn	Ornithine
PEG	Polyethylene glycol
Ph	Phenyl
PIP	Piperidine
PIFA	Phenyliodine bis(trifluoroacetate)
PMDTA	[Me ₂ N(CH ₂) ₂] ₂ NMe
RCM	Ring-closing metathesis
RT	Room temperature
S _N	Nucleophilic substitution
TBA	Tetra- <i>n</i> -butylammonium
TCR	Three component reaction
TEA	Triethylamine
TMEDA	Tetramethylethylenediamine
TMSN ₃	Trimethylsilyl azide
Ts	Tosyl

1 Introduction

Multicomponent reactions (MCRs) and domino reactions are increasingly important in organic and medicinal chemistry and are very powerful synthetic processes, because they allow to achieve both complexity and diversity of compounds in a single and simple experimental step with a high efficiency and atom economy, economies of time, labour, resource management, and waste generation. They offer significant advantages over conventional linear-type syntheses. The applicability of MCRs and domino reactions has been widely demonstrated in the synthesis of natural products and in medicinal chemistry. In recent years, several books and reviews have appeared, dealing with this issue [1–5].

By definition, multicomponent reactions are those reactions, where more than two reactants combine in a sequential manner, giving highly selective products where basically all or most of the atoms contribute to the newly formed product. In an MCR, a product is assembled according to a cascade of elementary chemical reactions. Thus, there is a network of reaction equilibria, which all finally come together into an irreversible step yielding the product. The challenge is to conduct an MCR in such a way that the network of pre-equilibrated reaction channels into the main product and does not yield side products. Such considerations are of particular importance in connection with the design and discovery of novel MCRs [6].

Unfortunately, there is no clear definition for domino reactions and similar meaning terms such as “cascade reactions” or “tandem reactions” are often used in the literature. Different authors use various definitions as to what constitutes a cascade process, although efforts have been made to restore order to this area of reaction terminology [7–13]. We consider the three most used definitions of “one-pot” multistage reaction processes. In such reactions, the substrate contains many functional groups that take part in chemical transformations one at the time. Firstly, if in a one-pot process two or more reactions proceed independently by different reaction centres, in such cases the term “tandem” is to be used. Secondly, if the reactions occur consistently without generating new reaction centres, these types of reactions are named cascade. Often a functional group is generated in situ from the previous chemical transformation. Such a process should be named as “domino type.” Although there is no unambiguous definition, it may safely be said that these reactions occur by the domino effect by pushing each other. Nevertheless, we believe that all of the above descriptions are an appropriate association of one group of domino reactions. A cascade reaction or tandem reaction or domino reaction is a consecutive series of intramolecular organic reactions which often proceed via highly reactive intermediates.

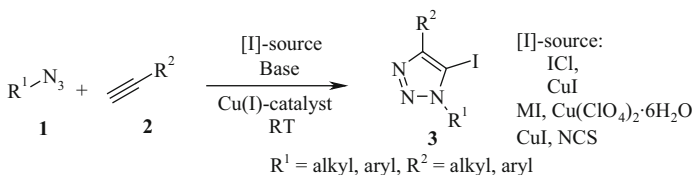
In conclusion, it is worth noting that MCRs and domino reactions have much in common and can be considered to fall under the concept of “green chemistry,” as savings are involved when one carries out several transformations in one synthetic operation [14, 15]. Moreover, in this review, we do not characterize all the benefits of these reactions but emphasize, in our opinion, their main advantages such as atom-economy, time-economy, more ecological-friendliness, facile handling and less hazards, because separation of the explosive, hazardous, and toxic intermediates and reagents is avoided. Finally, MCRs and domino reactions are perhaps the most promising and powerful methods for the generation of large molecule libraries in a parallel manner.

2 One-Pot Azide-Alkyne Cycloaddition with Subsequent Triazole Functionalization

We begin with a review of perhaps the largest section of the reactions, which are widely studied. Triazole chemistry, based on the philosophy and methodology of click reactions proposed by K. Barry Sharpless, received a very broad application [16]. The term “click chemistry” is proposed for the high yielding reactions that allow to create products that can be removed without chromatography, are stereo-specific, simple to perform, and can be conducted in easily removable or benign solvents. The azide-alkyne Huisgen cycloaddition with the use of a copper (Cu) catalyst at room temperature to a large extent falls under the click chemistry concept. Recently, a significant number of reviews, dedicated to the chemistry, different aspects of the synthesis and application of 1,2,3-triazoles, prepared by click reactions, have been published [17–27].

2.1 *One-Pot Azide-Alkyne Cycloaddition and Substituent Introduction of Substituents in Position 5*

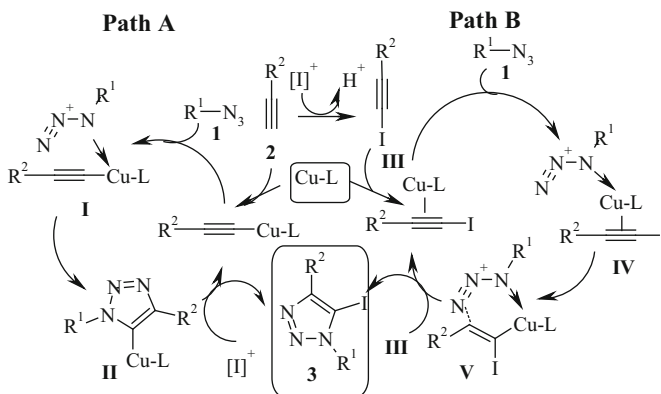
Obviously, taking into account an interest in triazole chemistry, based on a copper (I)-catalysed azide-alkyne cycloaddition (CuAAC), the philosophy of multicomponent one-pot processes should be used extensively. Indeed, a classic example of such a strategy is one-pot introduction of the substituent into the 5 position of triazole under the CuAAC conditions. One of the first examples representing this approach is a regiospecific synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazole **3** from azides **1** and alkynes **2** (Scheme 1). Such transformations are possible due to the fact that the intermediate copper(I) acetylide or Cu(I) salt of 1,2,3-triazole formed in CuAAC can be trapped by an electrophile [28]. In this way, a library of 5-iodinated 1,2,3-triazoles with aliphatic and aromatic substituents at the 1- and 4-positions in the presence of a variety of functional groups in the initial substrates were synthesized [19–33]. Iodination with ICl was selected for design, synthesis, and biological evaluation of 4,5-substituted 1,2,3-triazole derivatives, which are potential inhibitors of p38a MAP kinase. The starting azides were converted into the 4-aryl substituted 5-iodo-1,2,3-triazoles via the Cu(I)-catalysed [3 + 2] cycloaddition with 4-halogenated ethynylbenzene in THF–DCM and simultaneous iodination with ICl. It is to be noted that the reactions proceeded smoothly overnight in good yields (41–67%) as a one-pot two-step reaction with no intermediate purification [34]. This tactic applies to a large number of examples of different substituted azides, agents for the introduction of iodine, copper catalysts, and reaction conditions. For instance, the system of CuI and NBS was found to provide both I^+ and Cu^+ for an efficient preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles. It is claimed that the high tolerance of various sensitive groups revealed the potential applications of this method in organic synthesis and drug



Scheme 1 Three-component synthesis of 5-iodo-1,4-disubstituted-1,2,3-triazoles

discovery [35]. A significant number of studies were carried out by Fokin and colleges, dedicated to the synthesis of 5-iodo-1,2,3-triazoles via the regioselective reaction of iodoalkynes, prepared in situ with azides, using catalytic copper (I) iodide and a tris((1,2,3-triazolyl)methyl)amine ligand, such as tris((1-benzyl-1*H*-1,2,3-triazolyl)methyl)amine (TBTA). The 1-iodoalkyne was partially purified by filtration through neutral alumina prior to the introduction of the azide component. This method gave 5-iodotriazoles with efficiency comparable to that observed with the isolated 1-iodoalkynes [36, 37]. Moreover, it was shown that the above obtained 5-iodo-1,2,3-triazoles (Scheme 1) underwent facile substitution reactions with fluoride salts, thus providing ready access to 5-fluorotriazoles. The latter can be further elaborated with various nucleophiles to furnish fully substituted 1,2,3-triazole compounds [38]. Further elaboration can be used for the synthesis of a variety of 1,4,5-trisubstituted-1,2,3-triazole derivatives.

Smith et al. found that the identity of the organic base, as well as the concentration of the alkyne, could play major roles in determining the product nature in the CuI-promoted alkyne-azide cycloaddition (AAC). Low concentrations of the alkyne and the use of DMAP led to the formation of 5-I-triazoles as the only cycloaddition products [39]. Brotherton, Clark, and Zhu described the synthesis of 5-iodo-1,2,3-triazoles mediated by in situ generated copper(I) catalyst and electrophilic triiodide ion. Mixing copper(II) perchlorate and sodium iodide solutions results in copper(I) species and the electrophilic triiodide ions, which collectively mediate the cycloaddition reaction of organic azide and terminal alkyne to afford 5-iodo-1,4-disubstituted-1,2,3-triazoles. One molar equivalent of an amine additive is required for achieving a full conversion into 5-iodo-1,2,3-triazole by promoting the formation of 5-unsubstituted-1,2,3-triazole. Based on the preliminary kinetic and structural evidence, a mechanistic model is formulated in which a 5-iodo-1,2,3-triazole is formed via iodination of a copper(I) triazolide intermediate by the electrophilic triiodide ions (and possibly triethyliodoammonium ions). The experimental evidence explains the higher reactivity of the in situ generated copper (I) species and triiodide ion in the formation of 5-iodo-1,2,3-triazoles than that of the pure forms of copper(I) iodide and iodine [40]. An improved method has been developed for the preparation of 5-iodo-1,2,3-triazoles by a reaction mediated by copper(I) and iodinating agents generated in situ. The major methodological advance of the current procedure is that it provides a high conversion and good iodo/proto selectivity with a broad range of substrates without using an excess of the alkyne. The copper(II) perchlorate hexahydrate, used in the described work, was dried at 40–70°C in a vacuum oven overnight to remove adsorbed moisture (but not

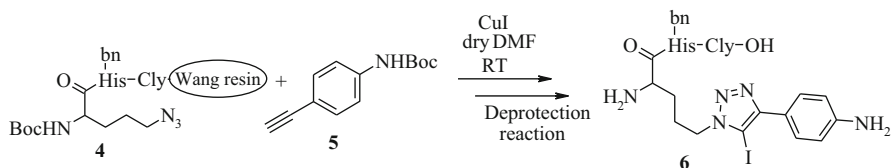


Scheme 2 Proposed mechanisms for the CuAAC including iodation reaction

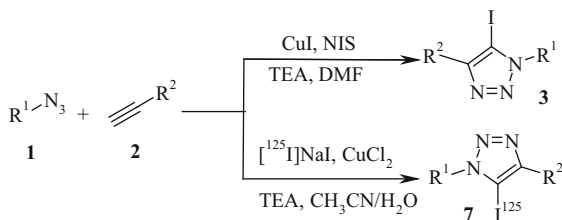
crystalline water) and subsequently stored in a dry keeper. The recommended procedure begins with the dissolution of the azide in tetrahydrofuran to give a 0.2 M solution. LiI (four equiv), $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (two equiv), triethylamine (one equiv), and the alkyne (one equiv) are then added sequentially. Coupling of an organic azide with a terminal alkyne in the presence of copper(II) perchlorate and an alkali metal iodide under mild conditions gives the corresponding 5-iodo-1,2,3-triazole. With the addition of the accelerating ligand TBTA (10 mol%), this procedure can tolerate a wide variety of functional groups, including carboxyl or hydroxy groups. Aliphatic and aromatic azides and alkynes can be readily converted into 5-iodo-1,2,3-triazoles with high to exclusive iodo/proto selectivity [41].

A possible mechanism for cascade cyclization and iodation was proposed by a number of chemists. The most accepted mechanism, outlined in Scheme 2, includes two pathways. One possible pathway (path A) is similar to that proposed for the CuAAC [27, 42, 43] and involves the formation of the σ -acetylide complex **I** as the first key intermediate. Coordination of the azide through the proximal nitrogen centre and subsequent cyclization yielded the cuprated triazoles **II**. Copper exchange through σ -bond metathesis with iodoalkyne **III** completes the cycle, thus liberating iodotriazole **3** and regenerating acetylide **2**. Alternatively (path B) [36], copper may activate the iodoalkyne **II** through the formation of a π -complex intermediate, which then engages the azide to produce complex **IV**. Cyclization then proceeds via a vinylidene-like transition state **V** to give iodotriazole **3**. A similar transition state has been proposed to explain the involvement of dicopper intermediates in the CuAAC reaction. The distinctive feature of this pathway is that the C–I bond is never severed during the catalysis.

Such a strategy is useful for the creation of complicated biocompounds. For instance, an efficient self-activating click reaction between azide- and acetylene-containing peptides on solid-phase has also been achieved by introducing the Nim-benzylhistidine residue on the reacting peptides. The reaction of Boc-Orn



Scheme 3 Representative example of solid-phase CuAAC-iodination reaction for peptide couplings

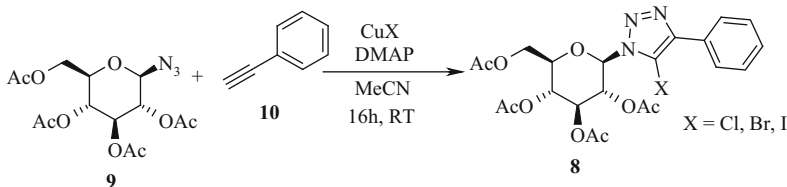


Scheme 4 One-pot three-component radiochemical synthesis of ^{125}I -labeled 1,2,3-triazoles

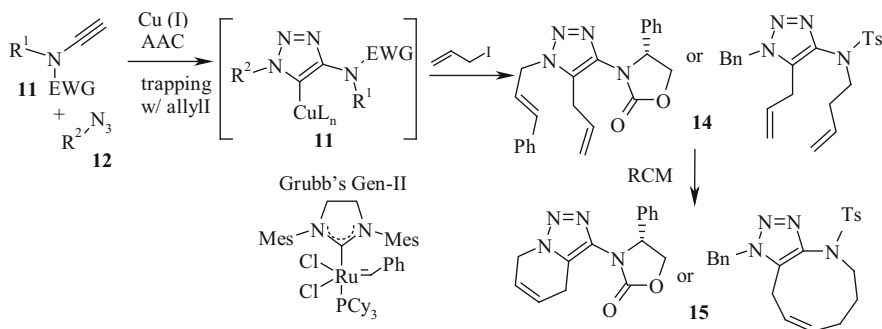
(N₃)-His(Bn)-Gly-OR **4** with N-Boc-4-ethynylaniline **5** provided the corresponding triazole **6** quantitatively (Scheme 3). The histidine-activated click reaction was applied to self-activating peptide couplings on solid-phase under additive-free conditions (Scheme 3) [44].

Furthermore, a one-pot three-component copper(II)-mediated reaction of azides **1**, alkynes **2**, and [^{125}I]iodide to yield 5- [^{125}I]iodo-1,2,3-triazoles **7** (Scheme 4) has been reported. Using a selection of azides and alkynes in a combinatorial approach, a library of structurally diverse ^{125}I -labeled triazoles, functionalized with bioconjugation groups, fluorescent dyes, and biomolecules, was created. Preliminary biological evaluation suggested that 5- [^{125}I]iodo-1,2,3-triazoles were resistant to deiodination in vivo, both as small molecular probes and as antibody conjugates. The ability to incorporate radioactive iodide into triazoles directly from the parent azides and alkynes makes the method broadly applicable and offers the potential to rapidly assemble molecular probes from an array of structurally diverse and readily available building blocks. The added flexibility of trisubstituted triazoles and their apparent resistance to metabolic deiodination has the potential to transform the development of tracers for biomedical imaging and therapeutic applications [45].

The above described method found a new accomplishment and development by using other electrophilic agents, including halogens. For example, a new synthetic protocol for the one-pot preparation of 5-halo-1,4-disubstituted-1,2,3-triazoles is provided by rational combination of a CuAAC reaction and an oxidative halogenation reactions. CuI-*N*-chlorosuccinimide (NCS) and CuBr-NCS reaction systems were developed, respectively, for effective preparation of 5-iodo-1,4-disubstituted-1,2,3-triazoles and 5-bromo-1,4-disubstituted-1,2,3-triazoles under mild conditions with a high tolerance of various sensitive groups [46, 47]. Moreover, new triazole-based compounds in accordance with the pocket binding requirements of human



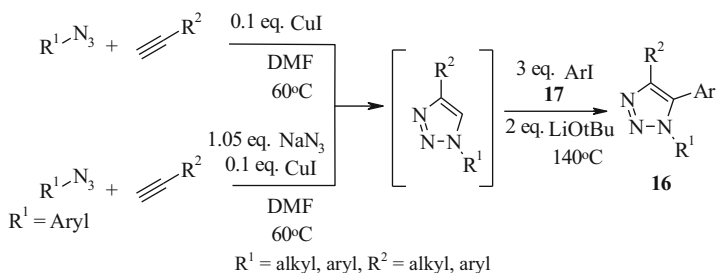
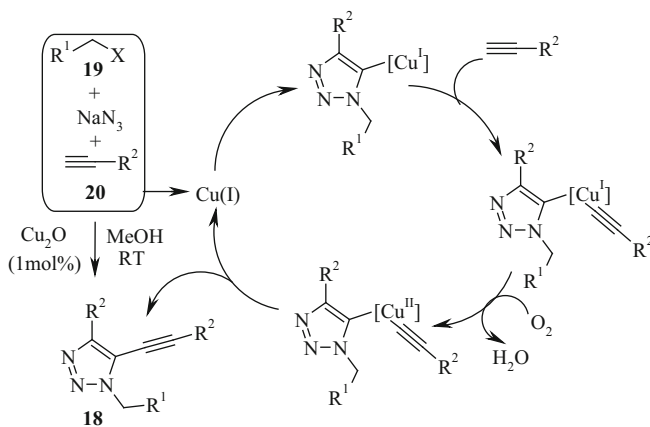
Scheme 5 Synthesis of 5-halogenated 1,2,3-triazoles **8** using stoichiometric amounts of Cu(I)-halides



Scheme 6 Fused triazoles via AAC (involving triazole alkylation with allyl iodide)

mPGES-1 were designed. Docking results, in agreement with ligand efficiency values, suggested the synthesis of compounds that at least in theory was shown to be more efficient in inhibiting mPGES-1. Biological evaluation of the selected compounds has disclosed three new potential anti-inflammatory drugs [48]. It is noteworthy that while catalytic amounts of copper halides provide specifically the 5-proto-1,2,3-triazoles, the introduction of an excess of CuX must be carefully controlled. Application of this synthetic methodology for the formation of 5-halogenated 1,2,3-triazoles **8** from azide **9** and phenylacetylene **10** in high yields (>74%) and under smooth conditions was reported for the design of potential glycogen phosphorylase inhibitors through Pd-catalysed C–C couplings (Scheme 5) [49].

Carbon–carbon bonds could also be formed in the course of the CuAAC reactions. The triazole copper intermediate **11** was generated in situ from azide **12** and alkyne **13** via [3 + 2] cycloaddition. The feasibility of trapping the intermediate **11** by allyl/propargyl iodide provided the preparation of 5-allyl/propargyl triazoles **14** in good yields. Such system can serve as a new template for ring-closing metathesis (RCM) to construct de novo fused triazoles **15**, which are otherwise non-trivial to access. The prepared triazoles **14** were examined in ring-closing metathesis using Grubb's Gen-II17 as a catalyst at room temperature yielding fused triazole **15** in excellent yield (Scheme 6) [50].

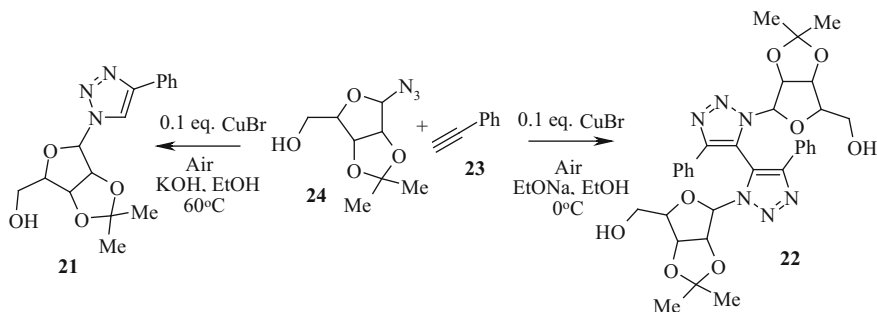
**Scheme 7** Sequent CuAAC and direct arylation**Scheme 8** One-pot synthesis of 5-alkynyl 1,2,3-triazoles **18** and proposed catalytic cycle

Lately, modular one-pot multicomponent synthesis of fully decorated triazoles **16** through a sustainable “click” reaction and direct arylation with iodoarenes **17** using inexpensive copper catalysts (Scheme 7) has been shown [51].

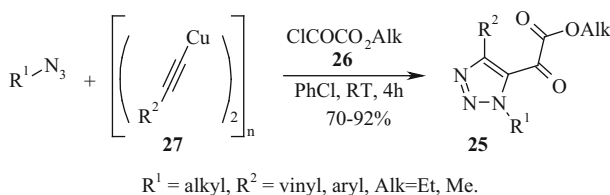
Moreover, copper(I) oxide was found to effectively catalyse the multicomponent click synthesis of fully substituted 5-alkynyl-1,2,3-triazoles **18** from organic halides **19**, sodium azide, and terminal alkynes **20** in methanol under ambient conditions. A possible mechanism of carbon–carbon bond formation was also proposed (Scheme 8) [52].

Angell and Burgess [53] have studied the condensation of acetylenes with various azides in the presence of Cu powder/CuSO₄ and aq. Na₂CO₃ in acetonitrile under air atmosphere at room temperature to obtain bistriazoles. A similar protocol was proposed for the controllable preparation of 1,2,3-triazoles **21** and bis(1,2,3-triazole)s **22** from alkyne **23** and azide **24** under different temperatures with good yields (63–91%). The reaction was successfully applied for nucleoside analogue synthesis (Scheme 9) [54].

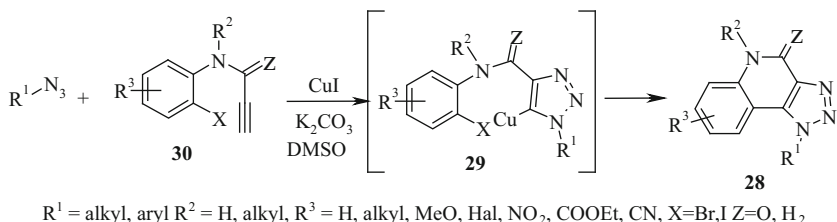
Recently, a novel one-pot three-component method has been discovered for an efficient preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazoles **25** via methodology by which the Cu–C bond in the 5-Cu(I)-1,2,3-triazole



Scheme 9 Temperature effect controlled synthesis of bis(1,2,3-triazole)s or 5-alkynyl-triazoles



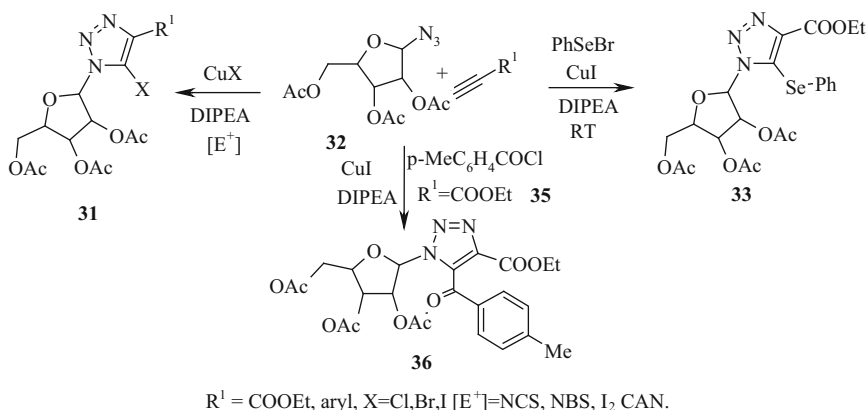
Scheme 10 Preparation of 1,4,5-trisubstituted 5-(2-alkoxy-1,2-dioxoethyl)-1,2,3-triazoles



Scheme 11 Tandem CuAAC/Ullmann coupling reactions of azides with *N*-(2-iodoaryl)-propiolamides or 2-iodo-*N*-(prop-2-ynyl)-benzenamines

intermediate (in situ formed) was trapped selectively by alkoxalyl chloride **26** in the presence of 1-Cu-alkyne (pre-made) **27**. It is important to note that the initial 1-Cu (I)-alkyne **27** does not react with alkoxalyl chloride **26** in solvent under base-free and ligand-free conditions since it is a metal cluster and has extremely high chemical stability (Scheme 10) [55].

The first combination of CuAAC and intramolecular Ullmann C–C coupling was reported for developing novel tandem reactions leading to the formation of 1*H*-[1,2,3]triazolo[4,5-*c*]quinolin-4(5*H*)-ones **28**. This occurred by the trapping of the C–Cu intermediate **29** produced in the CuAAC reaction (Scheme 11). The process proceeded efficiently when a variety of *N*-(2-iodoaryl)-propiolamides or 2-iodo-*N*-(prop-2-ynyl)benzenamines **30** were used, and it displayed a wide range of functional group compatibility (Scheme 11) [56].

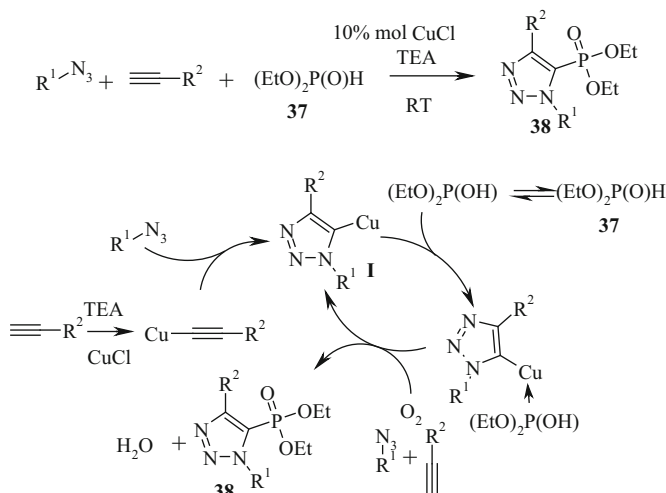


Scheme 12 The CuAAC–electrophilic addition tandem process

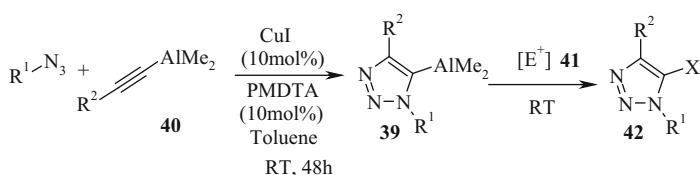
Malnuit and co-workers described a one-pot three-component approach to a new family of 4,5-functionalized triazolylnucleosides (Scheme 12). The method relies on a one-pot AAC/electrophilic addition tandem reaction, which affords good yields of the corresponding 4,5-disubstituted nucleosides **31**. In general, all reactions of NIS, NBS, and NCS with various azido-sugars **32** (α - and β -deoxy-ribose, D- and L-ribose and pyranose series) were performed. The CuCl/NCS and CuBr/NBS couples were used as sources of Cl^+ and Br^+ , respectively. It has also been found that this three-component reaction was applicable to other electrophiles. Thus, PhSeBr was used in the reaction for the 5-phenylselenide-substituted triazole **33** preparation in moderate yield, which is probably due to the low reactivity of the electrophile. Moreover, the reaction of azido-ribose **34**, ethyl propiolate **35** and toluoyl chloride, which was used as the electrophile, led to 5-toluoyl-triazolylnucleoside **36** in excellent yield [57].

Furthermore, by using a strategy of aerobic oxidative coupling, Cu/triazole complex **I** was successfully trapped by nucleophilic H-phosphonates **37** in a controlled manner to generate a variety of 1,2,3- triazoly1-5-phosphonates **38** (Scheme 13). This is the first example of the direct construction of a $\text{Csp}^2\text{-P}$ bond at room temperature through aerobic oxidative coupling reactions. In view of a high regioselectivity and efficiency, mild conditions, and applicability to a broad range of substrates bearing sensitive functional groups, this CuAA[P]C reaction (direct incorporation of P as accompanying a “click reaction”) provides a facile new protocol for the preparation of structurally sophisticated phosphorus compounds [58].

Finally, to make this current strategy more variable a way to the fixed Cu-triazole intermediate was demonstrated. Micouin et al. obtained aluminotriazoles **39** in a fully chemo- and regioselective manner by a copper-catalysed cycloaddition of organic azides with mixed-aluminum acetylides **40** (Scheme 14). The carbon–aluminum bond, unaffected by the first transformation, is still able to react further with different electrophiles **41** and enables a rapid and simple access to 1,4,5-trisubstituted triazoles **42** [59].



Scheme 13 Domino synthesis of 1,2,3-triazolyl-5-phosphonates and proposed catalytic cycle

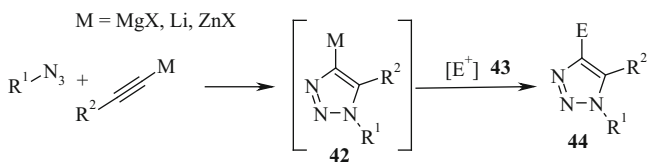


R^1 = alkyl, aryl R^2 = alkyl, aryl, $[E^+] = \text{DCl, D}_2\text{O; NCS, NBS, NIS, ClCO}_2\text{Alk; X=D, Cl, Br, I, CO}_2\text{Alk}$

Scheme 14 Synthesis of 1,4-disubstituted-5-alumino-1,2,3-triazoles and their one-pot transformation into 1,4,5-trisubstituted-1,2,3-triazoles

2.2 One-Pot Azide-Alkyne Cycloaddition and Substituent Introduction of Substituents in Position 4

The regioselective synthesis of 1,5-disubstituted 1,2,3-triazoles can be produced via the Huisgen cycloaddition of bromomagnesium acetylides to azides [60–62]. In 2004 Sharpless and co-workers upon the reexamination of an old process showed that the intermediates **42** of that reaction can be trapped with different electrophiles **43** and can regioselectively form 1,4,5-trisubstituted 1,2,3-triazoles **44** in a one-pot procedure (Scheme 15). The results of quenching of the 4-halomagnesium-1,5-diphenyl-1,2,3-triazole **43** with nine different electrophiles showed that yields are usually good, but in cases when trace acid impurities are hard to avoid, the product of protonation at C-4 is formed ($E = \text{H}$ in Scheme 15). It was also underlined that not all electrophilic compounds are suitable for this capture process. For example, the use of sulphamoyl and sulphonyl chlorides



R^1 = alkyl, aryl, RSO_2 ; R^2 = alkyl, aryl, $[\text{E}^+] = \text{DCl}, \text{D}_2\text{O}; \text{I}_2, \text{CO}_2, \text{ClCO}_2\text{Me}, \text{PhCOH}, \text{PhNCO};$
 $\text{E} = \text{D}; \text{I}, \text{CO}_2\text{H}, \text{CO}_2\text{Me}, \text{PhCHOH}, \text{PhNHCO}.$

Scheme 15 Synthesis of fully substituted 1,2,3-triazoles via the addition of bromomagnesium acetylides to azides with the following electrophilic attack

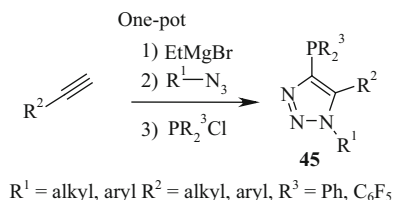
results in partial chlorination of the triazole ring at C-4. Although iodination with elemental iodine is an efficient process, the use of bromine promotes the formation of oxidatively coupled 4,4'-bis-triazoles in significant amounts, along with the 4-bromotriazole analogues. Because of the very strong basicity of 4-magnesiotriazoles, reactions with electrophiles, which also possess acidic C–H bonds, usually fail as a result of competing protonation at C-4 (Scheme 15) [63, 64]. In addition, it was found out that the reaction of lithium acetylides with sulphonyl azides, followed by trapping putative triazole anion with various electrophiles, yielded 1,4,5-trisubstituted sulphonyl triazoles **44** ($\text{R}^1 = \text{RSO}_2$ in Scheme 15) [65]. In both cases, the metallotriazole can react with several electrophiles, leading to 1,4,5-triazoles in a regioselective manner. The proposed mechanism involves a nucleophilic addition of the metal acetylide, followed by a ring closure to the metallotriazole. Moreover, the reaction of alkynylzinc or zincates with azides was reported to deliver metallotriazoles which can be further functionalized using a Negishi coupling reaction [66].

Lately, a simple one-pot three-step procedure, which allows the synthesis of a number of new members of mono(triazolyl)-phosphane ligands, has been reported. In the first step, the Grignard reagents were used to form the corresponding magnesium salts starting from an alkyne at low temperature. Subsequent addition of aryl or alkyl azides at slightly elevated temperature forms the triazolyl-magnesium salt. Direct treatment of these salts with various diarylchlorophosphanes furnished the triazoles **45** in moderate to good yields (Scheme 16) [67]. It is noteworthy that such triazole-based monophosphines **45** have been prepared previously via a multi-step procedure and studied as ligands in palladium complexes providing highly active catalysts for Suzuki–Miyaura coupling and amination reactions [68, 69].

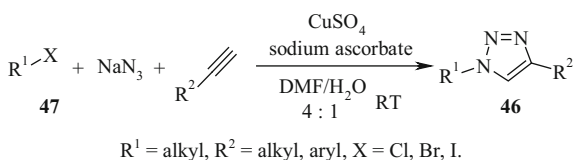
3 One-Pot Generation of Azides and Subsequent AAC Reactions

Synthesis, extraction, and purification of organic azides are dangerous, and difficult to handle procedures, so more advantageous and desirable are the methodologies in which the organic azides are generated in situ, avoiding their isolation. Such

Scheme 16 One-pot procedure towards 1,5-disubstituted-1*H*-1,2,3-triazol-4-ylphosphanes



Scheme 17 One-pot synthesis of 1,2,3-triazoles from alkyl halides, NaN_3 , and alkynes

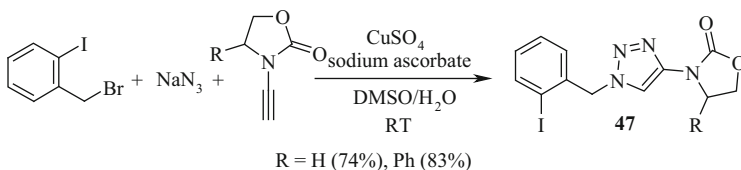


reactions are safer because hazards derived from their isolation and handling are minimized and time consuming and waste generating additional synthetic step is avoided. This is especially practical for small molecules with several azide functionalities.

3.1 Generation of Azides by the Nucleophilic Substitution or Addition Reaction and Subsequent AAC

One of the first multicomponent reactions, which avoided utilization of organic azides, was carried out by Fokin et al. [70]. By a convenient one-pot procedure, 1,4-disubstituted 1,2,3-triazoles **46** were obtained in excellent yields from a variety of readily available aromatic and aliphatic halides **47** without isolation of potentially unstable organic azide intermediates. Aliphatic azides can be readily prepared from the corresponding halides by nucleophilic displacement or, in case of aryl and vinyl azides, by a Cu(I)-catalysed reaction (vide infra) with sodium azide. The substitution is especially facile when activated halides, such as allylic, propargylic, and benzylic, are used (Scheme 17). Moreover, when this process was performed under microwave irradiation, the time of the reaction was significantly reduced [71].

This safe and efficient method for the synthesis of 1,4-disubstituted 1,2,3-triazoles became quite popular and widely used [72, 73]. A number of articles, where a variety of reagents and catalysts were tested in such an approach, have been published. For example, a one-pot synthesis of 1,2,3-triazole-linked glycoconjugates [74] or [1,2,3]-triazol-1-yl-trifluoroborates [75] from saccharide acetates or haloalkyltrifluoroborates correspondingly was performed. Afterward, tandem azidation- and hydroazidation-Huisgen[3 + 2]cycloadditions, employing chiral ynamides, were described [76] for the synthesis of chiral amide-substituted triazoles **47** (Scheme 18). It was noted that tandem processes are highly regioselective and chemoselective in the case of the hydroazidation of ynamides

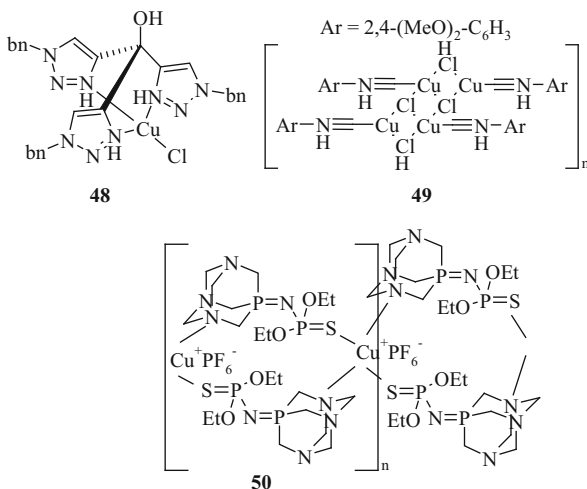


Scheme 18 A one-pot synthesis of amide-substituted triazoles from alkyl bromides and ynamides

[77]. A one-pot multicomponent click reaction was used to synthesize novel “drug-like” 1,2,3-triazoles in the eco-friendly conditions PEG-400/water (1:1, v/v) [78].

This reaction has been studied under different conditions varying the structure of the catalyst [79, 80]. For example, ultrasound-acceleration in water at room temperature, using CuI as a catalyst, was studied for such three-component reactions to form 1,4-disubstituted 1,2,3-triazoles. The authors claim that using water as the solvent and the purity of the recovered products makes it attractive not only for large-scale synthesis of this class of biologically active molecules but also for the synthesis of screening libraries for drug discovery [81]. Furthermore, a library of new 1,4-disubstituted 1,2,3-triazoles, with a variety of additional functional groups in their structure, from an in situ generated benzyl azide and different alkynes and dialkynes, was obtained by means of microwave-assisted synthesis in higher yields and in shorter times [82]. Later on, a new tris(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol ligand **48** (Fig. 1) was prepared by a triple Cu(I)-catalysed alkyne-azide 1,3-dipolar cycloaddition (CuAAC). Ligand **48** forms a stable complex with CuCl, which catalyses the Huisgen 1,3-dipolar cycloaddition in water or under neat conditions. Low catalyst loadings, short reaction times at room temperature, and compatibility with free amino groups make **48**·CuCl an outstanding catalyst for CuAAC in a one-pot process [83]. Looking for new catalysts, the protocols, where scientists use the cheap and easy-to-prepare Cu(PPh₃)₂NO₃ [84] and commercially available [CuBr(PPh₃)₃] [85] complexes, were elaborated. These systems are active at room temperature, with catalyst loadings of 0.5 mol% or less, in the absence of any additive, and it does not require any purification step to isolate pure triazoles. Moreover, it was shown [86] that a structurally well-defined copper(I) isonitrile complex **49** (Fig. 1) was an efficient, heterogeneous catalyst for a three-component preparation of 1,4-disubstituted 1,2,3-triazoles. The catalyst can be readily recovered by precipitation and filtration and recycled for at least five runs without significant loss of activity and applied to the cycloaddition reaction of electron-rich, electron-poor, hindered alkynes and dialkynes at room temperature in water to give the corresponding triazoles in high yields [86]. Finally, Garcia-Alvarez and co-workers demonstrated a new family of iminophosphorane Cu^I complexes related to **50** (Fig. 1), which exhibited a versatile and efficient catalytic activity in Huisgen three-component cycloaddition reaction of 1-iodoalkynes with azides in aqueous media under mild conditions. *N*-Thiophosphorylated iminophosphorane ligand was prepared by the treatment of water-soluble phosphanes 1,3,5-triaza-7-phosphaadamantane (PTA) and diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DAPTA) with an equimolecular amount of azides (RO)₂P(=S)N₃ (R = Et, Ph) [87].

Fig. 1 Structure of some catalysts for multicomponent CuAAC



The new catalytic systems enabled the development of regioselective, efficient, modular, mild, and eco-friendly multicomponent synthesis of diversely decorated 1,2,3-triazoles, contributing to expand the scope and versatility of the Cu-catalysed 1,3-dipolar cycloaddition. Application of ionic liquids in triazole multicomponent synthesis is interesting for green chemistry. It was shown that treatment of a copper (I) catalyst in a mixture of the ionic liquid [bmim][BF₄] and water can effect three-component reaction [88]. Moreover, it was found that the ionic liquid/H₂O is a good reaction medium for the synthesis of 1,2,3-triazoles using either halides at sp³-hybridized carbon atoms or halides at sp²-hybridized carbon atoms. This procedure permits extensive recycling of the solvent without substantial loss in activity within five times [88]. In addition, another one-pot procedure for 1,2,3-triazole preparation, catalysed by copper(I) and amino acid ionic liquid (AAIL) in [BMIM]BF₄, was developed by Jincan and Lei. It is noteworthy that CuI, AAIL, and [BMIM]BF₄ could be recovered after six consecutive trials without significant loss of activity. The reaction medium was prepared from [BMIM]OH and an appropriate amino acid such as L-proline, *trans*-4-hydroxy-L-proline, and *N,N*-dimethylglycine at room temperature, and the solution was then evaporated and dried in vacuo to generate the desired amino acid ionic liquids (AAILs) [89].

It is known that copper heterocyclic carbene complexes are a dynamically developing class of catalysts for the click reactions. These versatile and highly efficient catalysts for the Huisgen cycloaddition are represented in a number of articles. It was first demonstrated that in situ generated azides led to 1,2,3-triazoles with differently substituted alkynes in the presence of a [(NHC)CuBr] complex **51** (Fig. 2) (NHC = *N*-heterocyclic carbene) with extremely high reaction rates and excellent yields. Furthermore, for the first time an internal alkyne was successfully used in this copper-catalysed cycloaddition reaction. DFT calculations on this particular system allowed for the proposition of a new mechanistic pathway for disubstituted alkynes [90]. The use of a catalytic system, easily prepared in situ

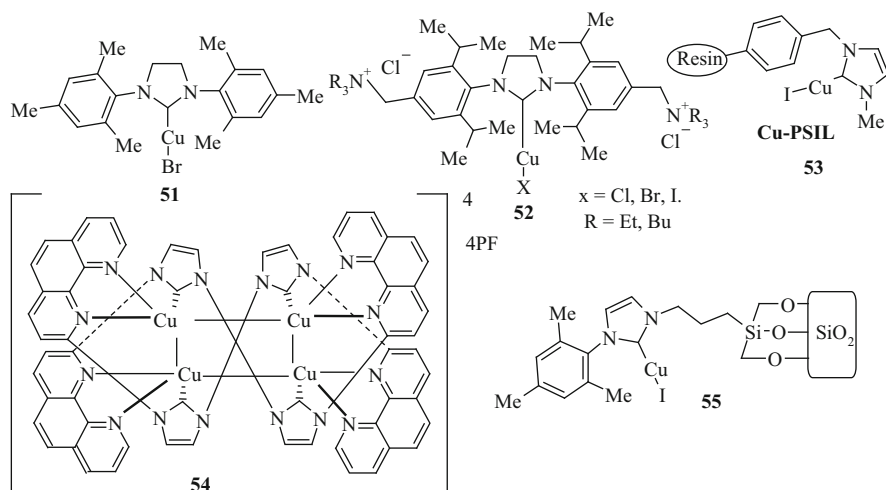


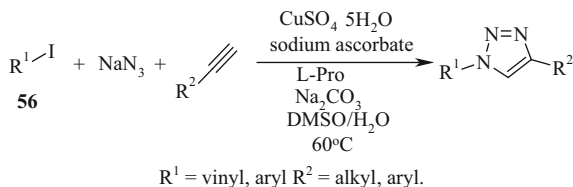
Fig. 2 Some copper heterocyclic carbene complexes for the CuAAC catalyst

from Cu(I) and Cu(II) species, in combination with benzimidazole salts in water medium provided many corresponding 1,2,3-triazole derivatives via a simple methodology [91]. Moreover, a series of ammonium salt-tagged SIPr ((SIPr = *N*, *N*′-bis(2,6-diisopropylphenyl)-imidazolidin-2-ylidene))–Cu(I) complexes **52** (Fig. 2) were conveniently synthesized, and it was observed that they were highly active toward three-component reaction (3CR). The current catalyst could be efficiently used at least four times with an 84% isolated yield of the desired triazole in the last run [92]. Moreover, Merrifield resin-supported copper (Cu-PSIL) and silica dispersed CuO (CuO/SiO₂) were selected as catalytic systems for the 3CR AAC. It was found that immobilized copper catalysts Cu-CPSIL **53** (Fig. 2) exhibited excellent catalytic activity for one-pot reactions. The X-ray photoelectron spectroscopy (XPS) results suggested that the supported Cu(II) catalysts were reduced to catalytic Cu(I) species via alkyne homocoupling reaction [93]. A rare macrocyclic tetranuclear copper (I) complex ($[Cu_4(2)_2](PF_6)_4$) **54** (Fig. 2) of phenanthroline-based NHC ligand was prepared and found to exhibit high catalytic activity in the CuAAC reaction in an air atmosphere at room temperature in a MeCN/H₂O mixture solution [94]. Furthermore, 1,2,3-triazole derivatives were synthesized in one-pot procedure in the presence of 0.5 mol% silica-immobilized NHC–Cu(I) catalyst **55** (Fig. 2). The copper catalyst immobilized on silica gel was readily prepared in a three-step procedure [95].

Solid state, silica functionalized nanoparticles and polymer supporting catalysis are also effective and useful for in situ azide generation and subsequent AAC reaction. For example, the dicopper-substituted γ -Keggin silicotungstate with bis- μ -1,1-azido ligands TBA₄H₂[γ -SiW₁₀O₃₆Cu₂(μ -1,1-N₃)₂] (**I**, TBA tetra-*n*-butylammonium) was used as an efficient precatalyst for the regioselective one-pot synthesis of various kinds of 1,4-disubstituted-1,2,3-triazole derivatives.

The catalyst effect, kinetic, mechanistic, and computational studies showed that the reduced dicopper core plays an important role in the present 1,3-dipolar cycloaddition [96, 97]. Furthermore, silica functionalized Cu(I) is reported as a green and recyclable heterogeneous catalyst for the regioselective synthesis of 1,4-disubstituted 1,2,3-triazoles via Huisgen 1,3-dipolar cycloaddition in water at room temperature. Silica functionalized Cu(I) could be recovered by simple filtration and recycled up to seven consecutive runs without loss of significant activity [98]. The mixed catalyst Cu(OAc)₂ on mobil composition of matter (MCM-41) showed a high catalytic activity and possibilities for the development of better catalysts supported on siliceous materials. These materials have a high surface area (1,000 m² g⁻¹), a large pore volume, and an ordered hexagonal pore array with pore diameters that can be tuned between 20 and 100 Å [99]. New supported catalysts have been prepared by immobilization of copper species on commercially available polymeric matrices incorporating the 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) template. The synergic exploitation of the exceptional copper chelating ability and basicity profile of the TBD framework, in addition to ensuring effective immobilization and stabilization of copper species, allows the implementation of three-component strategies [100]. Nanoferrites, post-synthetically modified by ligands, were used to immobilize nanometals (Cu, Pd, Ru, etc.), which enabled the development of efficient, sustainable, and green procedures for AAC. The beneficial attributes of such catalysts are an easy separation by an external magnet and their recovery and reuse. 1,4-Disubstituted 1,2,3-triazoles were synthesized by using magnetically separable and reusable copper ferrite nanoparticles (CuFe₂O₄) in high yields. The present method is simple, facile, and can be applied to a wide range of substrates with a high functional group tolerance [101]. The nm size range of these particles facilitates the catalysis process as an increased surface area is available for the reaction [102]. In addition, the copper nanoparticles on silica-coated maghemite nanoparticles (MagSilica[®]) were prepared under mild conditions by fast reduction of anhydrous CuCl₂ with lithium sand and a catalytic amount of DTBB (4,4'-di-tert-butylbiphenyl) as electron carrier, in the presence of the magnetic support [103]. The 1,2,3-triazoles were synthesized in water using magnetically recoverable heterogeneous Cu catalyst via one-pot multicomponent reaction using microwave irradiation [104]. A group of authors [105] demonstrated that a copper vial and copper ball can be used in lieu of a traditional homogenous copper catalyst to conduct the CuAAC reaction. As a catalyst for subsequent reactions, the recycled copper(II) sulphate, supported on ten alumina (Cu/Al₂O₃) under ball-milling in the absence of any solvent and additive, was used. This protocol offers a broad scope for an access to a variety of diversely substituted 1,2,3-triazoles in general with high yield. Several functional groups, such as F, Br, NO₂, CN, OMe, CO₂Et, CF₃, and CHO, are compatible under the reaction conditions. No rigorous extraction of the product by solvent and work-up are necessary [106]. For the first time, the potential of CuI-doped zeolites as heterogeneous catalysts was evaluated [107]. Furthermore, Cu^I-zeolites were found to be efficient heterogeneous catalysts for triazole synthesis [108]. At the same time, a lot of studies are dedicated to the

Scheme 19 One-pot synthesis of 1,2,3-triazoles from aryl and vinyl halides, NaN_3 , and alkynes

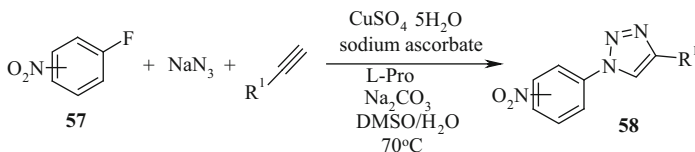
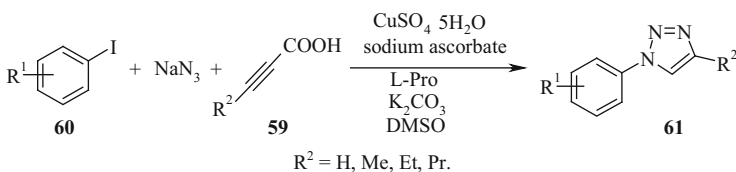


use of polymer supported copper nanoparticles. For instance, poly(4-vinyl pyridine) supported nanoparticles of copper(I) iodide were reported as green and recyclable catalysts, which can be recovered by a simple filtration and recycled up to eight consecutive runs without any loss of their efficiency [109, 110]. Moreover, self-assembly of copper sulphate and a poly-(imidazole – acrylamide) amphiphile was found to provide a highly active, reusable, globular, solid-phase catalyst for 3CR. The surface of the catalyst was covered with globular particles tens of nanometers in diameter, and those sheet-like composites were layered to build an aggregated structure. The imidazole units in the polymeric ligand coordinate with CuSO_4 to give a self-assembled, layered, polymeric copper complex. The catalyst was readily reused without loss of catalytic activity to give the corresponding triazoles quantitatively [111]. Finally, 3CR was performed in the presence of 1 mol% nanoparticles copper/carbon (Cu/C) catalyst [112]. It is noteworthy that zinc was also reported as a catalyst for 3CR AAC [113]. Moreover, it was shown that charcoal, impregnated with this zinc catalytic system, could tolerate a large variety of functional groups, including electron-rich and electron-poor substrates and heterocyclic alkynes [114].

It is worth noting that the S_N -CuAAC approach has a disadvantage that nucleophilic replacement of halides proceeds easily only in the case of activated halides, e.g., in benzylic or anomeric positions. A three-component one-pot S_N /click reaction was explored by employing aromatic compounds. Obviously, aryl azides can also be generated in situ using a modified Ullmann-type reactions and nucleophilic substitution in the aromatic ring ($\text{S}_\text{N}\text{Ar}$) reactions. The advantage of such a protocol is that both steps are catalysed by Cu(I). This reaction has been first demonstrated by Fokin et al. [70]. Aryl **56a**, heteroaryl **56b**, and vinyl **56c** halides readily participate in this process (Scheme 19) [115–117].

Otherwise, activated fluorobenzenes **57** reacted with azide nucleophile by the classic nucleophilic aromatic substitution ($\text{S}_\text{N}\text{Ar}$) mechanism resulting aryl azides, which underwent in situ Huisgen cycloaddition with alkynes for a rapid one-pot access to 1,4-substituted triazoles **58** (Scheme 20). The reactions are generally regioselective and various commonly employed protecting groups are found to be compatible with the employed conditions [118].

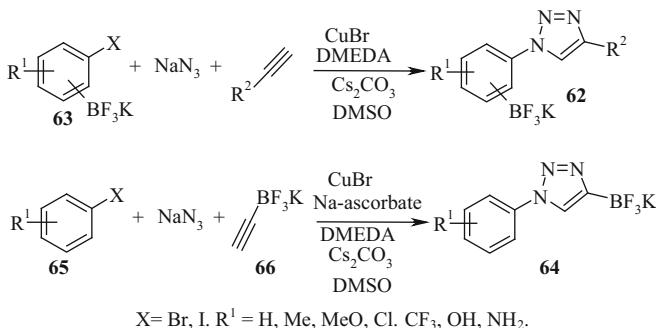
Ullmann-type reactions, including copper-catalysed nucleophilic aromatic substitution, have found wide application in three-component one-pot procedures. Such studies illustrate the feasibility and broad applicability of tandem catalysis processes. For instance, a tandem catalysis protocol was found based on decarboxylative coupling of alkynoic acids **59**. 1,3-Dipolar cycloaddition of

**Scheme 20** One-pot S_NAr -click reaction**Scheme 21** Tandem low molecular weight alkynes and aryl azides generated in situ for the synthesis of 1,2,3-triazoles

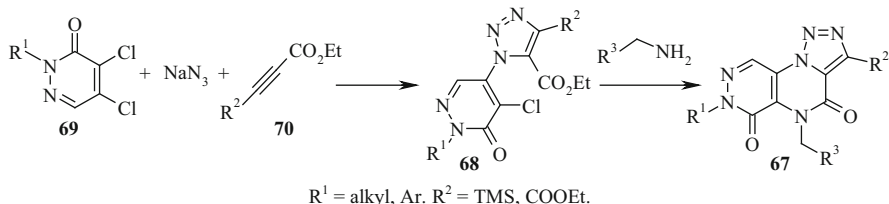
alkynes **59** and azides, prepared from aryl iodides **60**, enables the synthesis of a variety of functionalized 1,2,3-triazoles **61** (Scheme 21). The method avoids usage of gaseous or highly volatile terminal alkynes, reduces handling of potentially unstable and explosive azides to a minimum, and furnishes target structures in excellent yields and a very good purity without the need for additional purification. The decarboxylative protocol was found to tolerate a variety of structural patterns and yielded almost quantitative amounts of the target structures **61** in excellent purity. Substrates bearing either electron-donating or -withdrawing groups or even one of each type underwent smooth conversion, and the method turned out to be insensitive to unprotected carboxylic acid, amino, and phenol groups [119].

This type of reactions was expanded by the use of trifluoroborate reagents. Kim et al. elaborated a method for the regiospecific preparation of organo-[1,2,3]-triazol-1-aryl-trifluoroborates **62** from haloaryltrifluoroborates **63** via a one-pot 1,3-dipolar cycloaddition reaction (Scheme 22). It should be mentioned that the use of either electron-rich or electron-deficient haloaryltrifluoroborates led to the desired cycloaddition products with good to excellent yields [120]. Furthermore, a novel series of 1,4-disubstituted 1,2,3-triazole-containing potassium trifluoroborates **64** were prepared in good to excellent yields from the corresponding organohalides **65** and potassium ethynyltrifluoroborate **66** (Scheme 22). This method allows a convenient access to versatile triazole-containing trifluoroborate reagents, a class that can be difficult to obtain by other means [121]. Subsequent Suzuki–Miyaura cross-coupling of these 1,2,3-triazolo trifluoroborates with aryl and alkenyl bromides was demonstrated.

In addition, copper nanoparticles on activated carbon were found to effectively catalyse the multicomponent synthesis of 1,2,3-triazoles from different azide precursors, such as organic halides, diazonium salts, anilines, and epoxides in water [122]. The activity of different catalysts was tested in the cycloaddition of benzyl bromide and phenylacetylene. It was determined that the best results were obtained



Scheme 22 One-pot preparation of 1-aryl-1*H*-1,2,3-triazoles containing a potassium trifluoroborate moiety

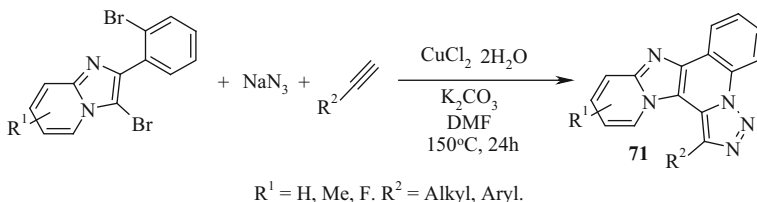
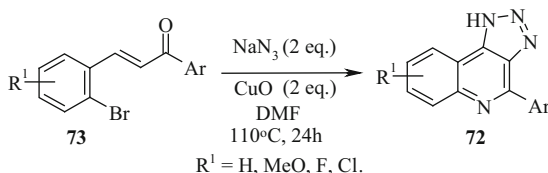
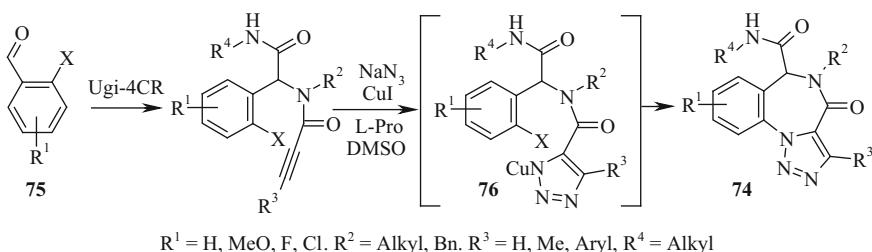


Scheme 23 One-pot synthesis of the substituted [1,2,3]triazolo[1',5':1,6]pyrazino[2,3-*d*]pyridazine-4,6(5*H*,7*H*)-dione

with SiO₂, Al₂O₃, Al silicate, magnetite, graphite, multi-walled carbon nanotube, and activated carbon. Among them, the activated carbon exhibited the highest activity (>99% yield, 3 h), giving triazole in quantitative yield after reuse in a second cycle [123].

The proposed multicomponent strategy S_NAr-AAC is suitable for the synthesis of fused aromatic rings. For example, [1,2,3]triazole-fused pyrazinopyridazinone tricycles **67** were synthesized in a four-component stepwise condensation with 42–73% isolated yields (Scheme 23). The key step in this one-pot process was a thermal [3 + 2] triazole **68** formation (by 3CR from 4,5-dichloropyridazinones **69**, sodium azide, diethyl acetylenedicarboxylate **70**), which activated the adjacent position and set the stage for a subsequent tandem nucleophilic aromatic substitution/cyclization sequence. It should be noted that a limitation of this protocol was observed with more sterically demanding primary amines, such as *t*-butyl amine and α -methylbenzylamine [124].

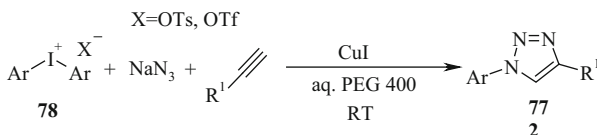
On the other hand, a ligand-free copper-catalysed tandem CuAAC, Ullmann-type C–N coupling, and intramolecular direct arylation were described. Such a protocol led to a novel triazole-fused azaheterocycle framework. The reaction gave good yields of 1,2,3-triazole-fused imidazo[1,2-*a*]pyridines **71** in a single step (Scheme 24) [125].

**Scheme 24** Tandem synthesis of 1,2,3-triazole-fused imidazo-[1,2-*a*]pyridines**Scheme 25** One-pot synthesis of 4-substituted 1*H*-[1,2,3]triazolo[4,5-*c*]quinolines**Scheme 26** Tandem CuAAC/Ullmann C–N coupling for the synthesis of triazolo[1,5-*a*][1,4]benzodiazepinones

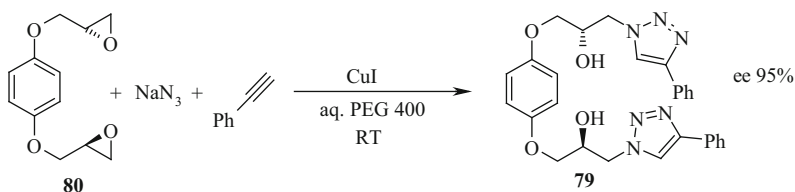
Furthermore, a protocol for the synthesis of 4-substituted-1*H*-[1,2,3]triazolo[4,5-*c*]quinolines **72** through a CuO-promoted tandem cyclization reaction was developed from the readily available (*E*)-3-(2-bromoaryl)-1-arylprop-2-en-1-ones **73** and sodium azide (Scheme 25) [126].

An attractive synthetic way, as a combination of the tandem azide–alkyne cycloaddition/Ullmann C–N coupling with Ugi 4-component reaction, was elaborated and is shown in Scheme 26. The methodology is compatible with various functional groups and allows the construction of triazolo[1,5-*a*][1,4]benzodiazepinones **74** starting from 2-haloarylcarbaldehydes **75** in good yields by the intramolecular trapping of the N–Cu intermediate **76**, formed by the CuAAC, by Ullmann coupling leading to the formation of the C–N bond [127].

Besides the halides, several other function groups could be used for three-component one-pot S_N -click reaction. Kumar and Buchi Reddy described the synthesis of 1,4-diaryl-1*H*-1,2,3-triazoles **77** via the reaction of diaryliodonium salts **78**, sodium azide, and terminal alkynes (Scheme 27). The best result for the in situ



Scheme 27 One-pot synthesis of 1,4-diaryl-1*H*-1,2,3-triazoles from diaryliodonium salts

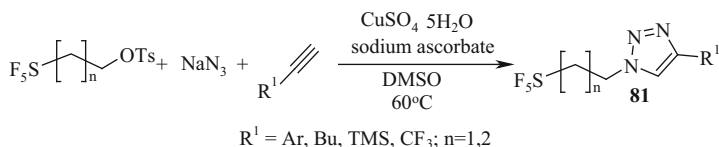
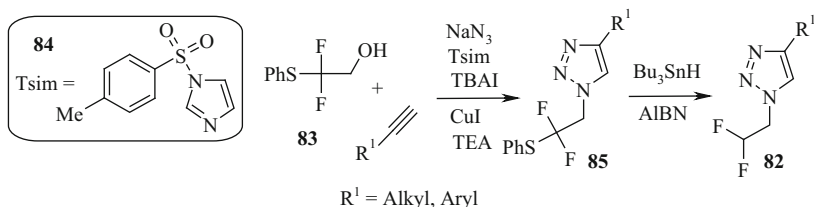


Scheme 28 One-pot synthesis of aryloxy α -hydroxy triazoles

generation of phenyl azide was obtained using copper(I) iodide in PEG 400–water (1:1, v/v) solution at room temperature. Notably, as a result of the weak nucleophilicity of the counter anions and their high solubility, both diphenyliodonium triflate and diphenyliodonium tosylate salts were suitable and equally reactive starting materials for the in situ generation of azides in good yield [128].

Epoxides are commonly used as starting materials in 1,2,3-triazole preparation. For example, the synthesis of α -hydroxy or *N*-tosylamino 1,2,3-triazoles **79** via azidation of epoxides **80** or *N*-tosylaziridines with sodium azide followed by AAC using PEG-400 as a reaction medium in the presence of 5 mol% of CuI, was described (Scheme 28) [129]. Enantiomerically pure epoxide and *N*-tosylaziridines were obtained in high yield with excellent *ee* values maintaining stereospecificity [130]. The efficiency of the reaction can be increased by using a new heterogeneous catalyst. For example, the latter was prepared by simple and successful impregnation of the catalyst onto activated multi-walled carbon nanotubes [131]. Additionally, copper(I)-modified zeolites, especially CuI-USY, proved to be very efficient catalysts in multicomponent reactions of epoxides [132].

Furthermore, compounds containing mesyl- or tosyloxy function groups are simple and convenient precursors for a one-pot regioselective synthesis of 1,4-disubstituted-1*H*-1,2,3-triazoles. For instance, fused triazoles with a bis-azahomotwistane skeleton were prepared via tandem reactions of the activated *cinchona* alkaloids with azide ion in a subsequent intramolecular alkyne-azide cycloaddition (IAAC) [133]. Moreover, a wide range of α -tosyloxy ketones and acetylenic compounds were tested for preparation of the assembly of a diverse set of 1,4-disubstituted-1*H*-1,2,3-triazoles [134]. In the same manner, 1,2,3-triazoles **81** containing the pentafluorosulphanylalkyl group were synthesized in good to excellent yields. Noteworthy, isolation of such azides as SF₅-ethyl azide is hazardous due to its low boiling point and high nitrogen content (Scheme 29) [135].

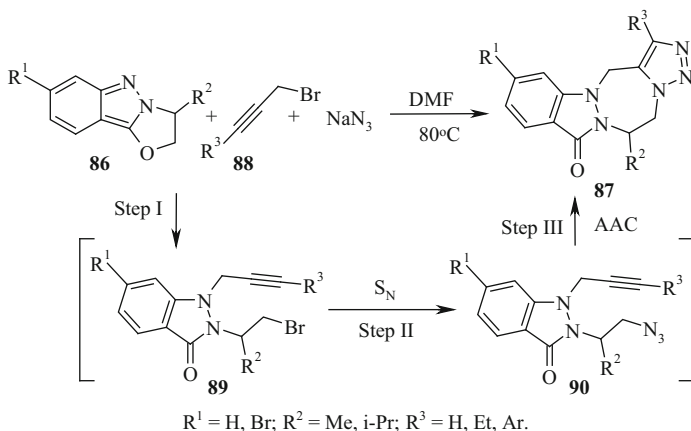
**Scheme 29** One-pot preparation of 1,4-disubstituted 1,2,3-triazoles via click chemistry**Scheme 30** *N*-(*p*-Toluenesulphonyl)imidazole activator for S_N -AAC reaction

Moreover, fourteen difluoromethyl-containing 1,4-disubstituted 1,2,3-triazoles **82** were synthesized via the reaction of 2,2-difluoro-2-phenylsulphanylethanol **83**, sodium azide and terminal alkynes in the presence of *N*-(*p*-toluenesulphonyl)imidazole **84**, tetrabutylammonium iodide and triethylamine, followed by reductive cleavage of the phenylsulphonyl group in **85** using tributyltin hydride and azobisisobutyronitrile (Scheme 30) [136].

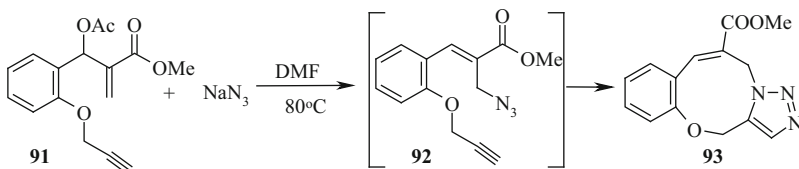
Conrad and co-workers developed a one-pot three-step method for the conversion of oxazolino-2*H*-indazoles **86** into triazolotriazepinoindazolones **87** with three points of diversity. Step one of this process involves a propargyl bromide **88**-initiated ring opening of the oxazolino-2*H*-indazoles **86** (available by the DavisBeirut reaction) to give an *N*¹-(propargyl)-*N*²-(2-bromoethyl)-disubstituted indazolone **89**, which then undergoes CH_2Br to CH_2N_3 displacement (step two, **90**) followed by an uncatalysed intramolecular azide-alkyne 1,3-dipolar cycloaddition (step three) to form the target heterocycle **87** (Scheme 31) [137].

Acetylated Baylis–Hillman adducts were found to be useful starting materials for 3CR, leading to 1,4-disubstituted 1,2,3-triazoles [138, 139]. Recently, Baylis–Hillman adducts have been used to provide IAAC, which led to fused triazoles. Novel tricyclic [1,2,3]-triazolo-[1,4]-benzoxazonine derivatives were obtained from the Baylis–Hillman acetates **91** by the treatment with sodium azide followed by heating the resulting azido-alkyne **92** for 2 h at 110°C in the same solvent to provide **93** in overall 55% isolated yield in the absence of any copper salts (Scheme 32). However, authors emphasized that the two-pot operation process, with the second step using toluene as a solvent (under reflux), gave high yields [140].

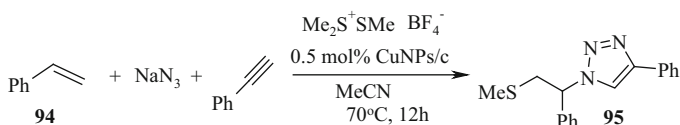
Alkenes could also be used as starting materials in one-pot protocols for 1,2,3-triazole synthesis. For instance, by the Michael addition of azide ion to α,β -unsaturated ketones and subsequent 1,3-dipolar reaction, 1,2,3-triazoles were prepared in very short times (30 min to 1 h) and satisfactory yields



Scheme 31 One-pot three-step synthesis of variously substituted triazolotriazepinoindazolones



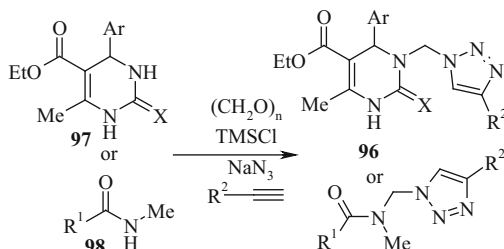
Scheme 32 One-pot synthesis of [1,2,3]-triazolo-[1,4]-benzoxazone



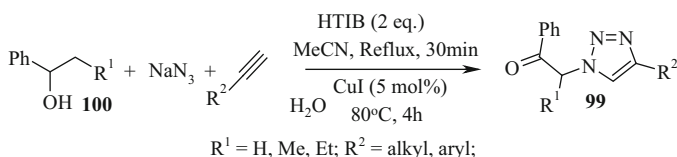
Scheme 33 One-pot protocol for the synthesis of 1,2,3-triazoles starting from inactivated alkenes

[141]. Furthermore, starting from inactivated alkenes **94**, and using a one-pot two-click process, the azidosulphenylation of the carbon–carbon double bond and the CuAAC led to the β -methylsulphenyl triazoles **95**, which were obtained using CuNPs/C as a catalyst (Scheme 33) [142]. The versatility of the methylsulphenyl group has been demonstrated through a series of synthetic transformations, including the direct access to 1-vinyl and 4-monosubstituted triazoles.

Recently, a one-pot CuAAC reaction combined with a Mannich addition has been reported. A series of N-functionalized 1,2,3-triazoles **96** with 3,4-dihydropyrimidione or amide fragment was prepared by the Cu(I) (generated in situ from $\text{Cu}(\text{OAc})_2 \cdot 3\text{H}_2\text{O}$ /sodium ascorbate) catalysed one-pot MCR of 3,4-dihydropyrimidiones **97** or amides **98**, paraformaldehyde, sodium azide, and alkynes (Scheme 34) [143].



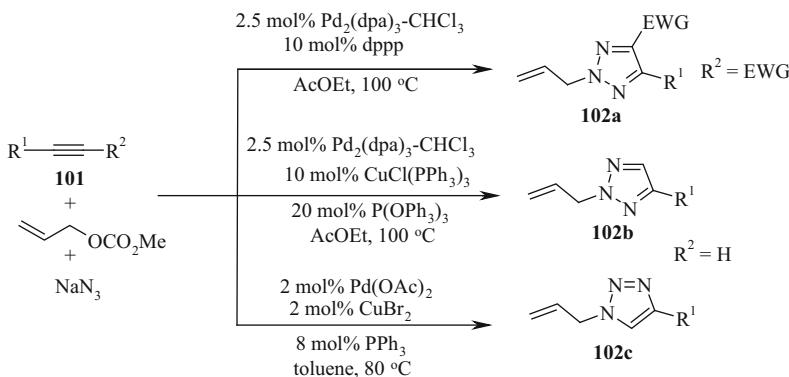
Scheme 34 Sequential Mannich-CuAAC synthesis of functionalized 1,2,3-triazoles



Scheme 35 Synthesis of β -keto-1,2,3-triazoles from secondary alcohols

An efficient method for the synthesis of 1,2,3-triazoles (β -keto-1,2,3-triazoles) **99** in good to excellent yields by successive treatment of secondary alcohols **100** with [hydroxy(tosyloxy)iodo]benzene (Koser's reagent) and sodium azide, followed by AAC, was described (Scheme 35). The reaction includes the direct conversion of an alcohol with HTIB into a tosyloxyketone intermediate, which, without isolation, was treated with sodium azide and phenylacetylene, using copper(I) iodide as a catalyst to furnish the β -keto-1,2,3-triazole in an one-pot operation. It was underlined that water plays an important role in this reaction for (a) quenching of HTIB; (b) formation of azide nucleophile; and (c) formation of copper acetylide from copper iodide and acetylene without any amine base [144].

Finally, Yamamoto et al. proposed a unique synthetic route for 2*H*-1,2,3-triazoles using a multicomponent protocol. By the palladium-catalysed 3CR of alkynes **101**, allyl methyl carbonate and trimethylsilyl azide 2-allyl-1,2,3-triazoles **102 a,b** were prepared (Scheme 36) [145]. For example, the reaction of phenylacetylene with allyl methyl carbonate and TMSN_3 was carried out in AcOEt at 100°C under the $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3\text{-P(OPh)}_3\text{-CuCl(PPh}_3)_3$ catalyst system. The reaction was completed in 10 h to afford 2-allyl-4-phenyl-1,2,3-triazole in 83% yield [146]. Notably, the cooperative activity of palladium and copper catalysts plays an important role in the present transformations. To accomplish the regioselective synthesis of the allyltriazoles, proper choice of two different catalyst systems is needed. The combination of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 - \text{CuCl(PPh}_3)_3 - \text{P(OPh)}_3$ catalyses the formation of 2-allyl-1,2,3-triazoles **102b**, while the combination of $\text{Pd(OAc)}_2 - \text{CuBr}_2 - \text{PPh}_3$ promotes the formation of 1-allyl-1,2,3-triazoles **102c** (Scheme 36). Authors also proposed a plausible mechanism for the allyltriazole forming reaction using a Pd(0)-Cu(I) bimetallic catalyst



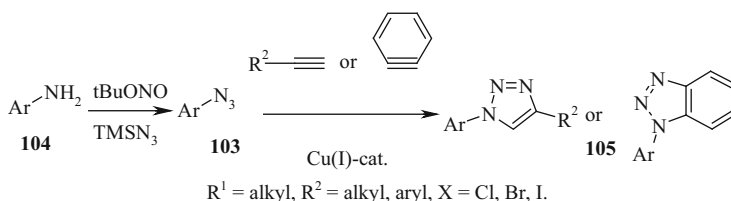
Scheme 36 Synthetic route for allyl 1,2,3-triazoles using MCR

[147]. In conclusion, fully substituted triazoles were synthesized via the four-component coupling reaction of unactivated silylacetylenes, two equivalents of allyl carbonates, and trimethylsilyl azide in the presence of a Pd(0)–Cu(I) bimetallic catalyst [148].

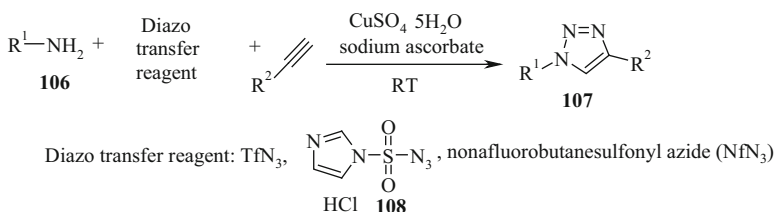
3.2 One-Pot Generation of Azides from Amines and CuAAC Reactions

Another convenient class of precursor for the preparation of organic azides preparation are amino derivatives. It is not surprising that they are also used in multicomponent processes. A simple and highly efficient procedure for the conversion of aromatic amines into their corresponding azides is using stable and non-explosive reagents, such as *tert*butyl nitrite (*t*-BuONO) and azidotrimethylsilane (TMSN₃). Barral and co-workers elaborated a methodology for a one-pot preparation of azides **103** from amines **104** and subsequent “click-reaction,” enabling an access to 1,2,3-triazoles **105** without the need to isolate the corresponding aromatic azide. This procedure should prove to be especially useful when unstable low molecular weight and polyvalent aromatic azides are needed (Scheme 37) [149]. Moreover, a modification of this methodology, using microwave radiation to significantly enhance the rate of formation of 1,4-disubstituted triazoles, was reported [150]. The above methodology was also used for the synthesis of substituted benzotriazoles (Scheme 37). In addition, it was found that heating the reaction with microwave irradiation dramatically decreased reaction times from hours to minutes with yield increase in some cases [151].

Another widely used approach to the synthesis of azides is the diazo transfer reaction. In 2007, Beckmann published a one-pot two-step procedure involving generation of azides *in situ* from primary amines **106** via Cu(II)-catalysed diazo



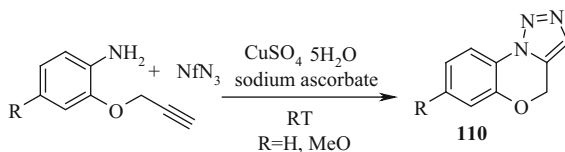
Scheme 37 Conversion of aromatic amines into azides by using of *t*-BuONO and TMSN₃



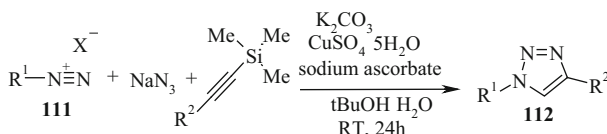
Scheme 38 One-pot diazo transfer-CuAAC reactions

transfer and Cu(I)-catalysed azide-alkyne 1,3-dipolar cycloaddition, which led to 1,2,3-triazoles **107**. The first step was the preparation of series of azides from various primary amines using triflic azide (TfN₃) in combination with copper (II) sulphate and solid sodium bicarbonate. After complete conversion into azide, acetylene and the reducing agent were added directly without any work-up procedure to provide the CuAAC reaction [152]. Later, as an effective heterogeneous catalyst for tandem diazo transfer process, click reactions mediated by trifluoromethanesulphonyl azide and copper-in-charcoal (Cu/C) were proposed [153]. Smith et al. underlined several practical limitations for the use of TfN₃ and focused on its explosive nature. The latter makes difficult to apply the reagent in parallel or combinatorial synthesis. On the contrary, it was proposed to utilize the inexpensive, shelf-stable diazo transfer reagent imidazole-1-sulphonyl azide hydrochloride **108** in a one-pot procedure for the regioselective synthesis of the functionalized 1,4-disubstituted 1,2,3-triazoles from primary amines (Scheme 38). The procedure is experimentally simple and suitable for parallel chemistry [154]. In addition, the diazo transfer approach allows to synthesize fused triazole derivatives. Nonafluorobutanesulphonyl azide is an efficient, shelf-stable, and cost-effective diazo transfer reagent for the synthesis of azides from primary amines. The nonafluorobutanesulphonyl azide was successfully applied to a one-pot regioselective synthesis of 1,2,3-triazoles, including intramolecular variants leading to polycyclic derivatives **110**, from primary amines by sequential diazo transfer and azide-alkyne 1,3-dipolar cycloaddition process (Scheme 39) [155].

Lately, Fletcher and Reilly have examined whether the commercially available diazonium salts **111** could be used as efficient aromatic azide precursors in one-pot multi-step click transformations. Seven different diazonium salts, including Fast Red RC, Fast Blue B, Fast Corinth V, and Variamine Blue B, were surveyed under



Scheme 39 One-pot synthesis of 4*H*-[1,2,3]triazolo[5,1-*c*][1,4]benzoxazine from amine

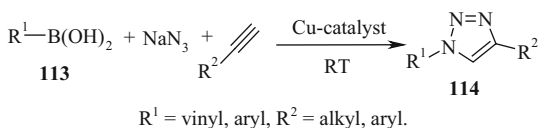
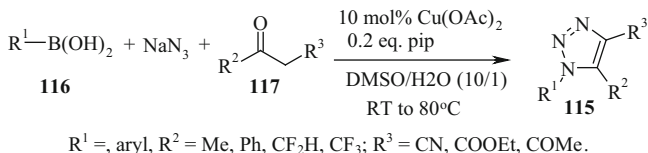


Scheme 40 Diazonium salts as aromatic azide precursors for 3CR CuAAC

aqueous click reaction conditions of $\text{CuSO}_4/\text{Na ascorbate}$ catalyst with 1:1 *t*-BuOH/ H_2O solvent and led to 1,2,3-triazoles **112** in 61–88% yields (Scheme 40). These findings establish diazonium salts as new and practical additions to a recently evolving class of synthons able to generate organic azide intermediates in situ [156].

3.3 Generation of Azides from Boronic Acids and the Following Triazole Formation

Synthesis of azides from boronic acids is a relatively new, but very promising and convenient approach for three-component 1,2,3-triazoles preparation. Recently, such an approach has been used to synthesize aryl and vinyl azides from the corresponding boronic acids **113** and a one-pot approach has been applied to synthesize 1-aryl- and 1-vinyl-1,2,3-triazoles **114** (Scheme 41). It was found that the proposed azidation reaction occurred smoothly in the presence of several different Cu salts including $\text{Cu}(\text{OAc})_2$, CuSO_4 , CuI , and CuCl [157]. Various reaction conditions and catalytic systems can be used in such a reaction. For example, montmorillonite KSF clay supported CuO nanoparticles found to be efficient catalysts in one-pot aromatic azidation of aryl boronic acids followed by the CuAAC reaction producing corresponding 1-aryl-1,2,3-triazole derivatives at room temperature [158]. Finally, magnetically recoverable and reusable CuFe_2O_4 nanoparticles were shown to be highly efficient catalysts for a one-pot synthesis of biologically important 1,4-diaryl-1,2,3-triazoles. Usage of aqueous reaction medium at room temperature, the low cost and facile recovery of the catalyst by application of an external magnetic field, and consistently high catalytic efficiency for at least three consecutive cycles render the protocol operationally attractive [159].

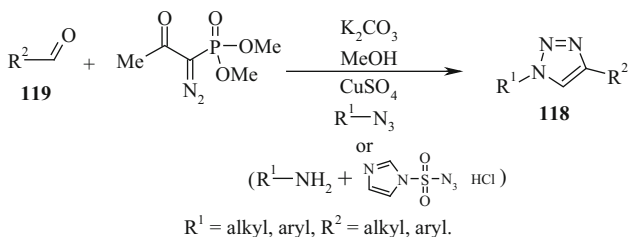
**Scheme 41** Synthesis of 1,4-diaryl-1,2,3-triazoles from boronic acids**Scheme 42** One-pot synthesis of 1,4,5-trisubstituted 1,2,3-triazoles from boronic acids

One of the main advantages of using boronic acids as azide precursor is the possibility to use them in cyclocondensation reactions with β -keto esters. The latter, in contrast to alkynes, are much less studied and allow regioselective introduction of substituents at position 5 of the triazole ring. Thus, a series of 1-aryl-5-trifluoromethyl (or difluoromethyl) 1,4,5-trisubstituted 1,2,3-triazoles **115** were synthesized in high yield by a novel one-pot three-component reaction of arylboronic acids **116**, sodium azide, and active methylene ketones **117**, such as ethyl 4,4-difluoroacetoacetate or ethyl 4,4,4-trifluoroacetoacetate in the presence of Cu(OAc)_2 and piperidine using a $\text{DMSO/H}_2\text{O}$ (10/1) mixture as a solvent (Scheme 42) [160].

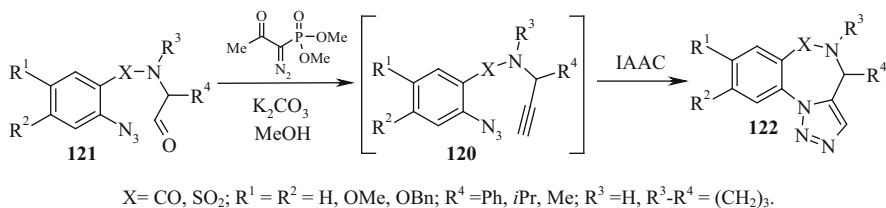
In summary, the reaction of in situ generated azides followed by CuAAC is a useful synthetic approach helping in the creation of compounds directed at different targets. For example, recently the generation of alkyl, benzyl, or aryl substituted bi- and tridentate pyridyl-1,2,3-triazole ligands [161], compounds with cytotoxicity activity [162], and other compounds assigned for biological activities screening research have been prepared [163, 164].

4 Generation of Alkynes with a Following AAC Reaction

Besides multicomponent strategies relying on in situ generation of the azido group, there are a large number of reports, focusing on the creation or modification of triple bonds or functionalization of substrates containing reactive groups for the synthesis of triazoles.



Scheme 43 One-pot reaction of terminal alkynes generation-AAC reaction



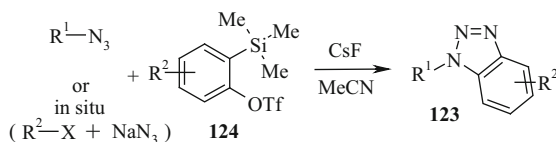
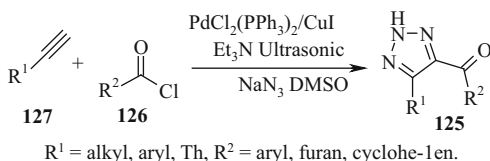
Scheme 44 Synthesis of 1,2,3-triazolo fused 1,4-benzodiazepines, 1,2,5-benzothiadiazepines, pyrrolobenzodiazepines, and pyrrolobenzothiadiazepines from the corresponding aldehydes

4.1 Tandem Ternary Bond Formation in AAC Reactions

The usage of the Ohira–Bestmann reagent (dimethyl-1-diazo-2-oxopropylphosphonate) in the Seyferth–Gilbert homologation reaction for the generation of terminal alkynes at low temperatures allows to combine this methodology in a one-pot AAC protocol. Such a reliable and operationally simple one-pot reaction for a one-carbon homologation provided 1,4-disubstituted 1,2,3-triazoles **118** in good to excellent yields from a variety of readily available aldehydes **119** without the need for isolation of the alkyne intermediates (Scheme 43) [165]. The reaction has a broad scope, allows the formation of new bioconjugates, and has been applied for the synthesis of new boronic acid-based fluorescent sensors [165], fluorescent amino acid derivatives as well as glycoconjugate mimetics [166]. The above-mentioned approach was used for the synthesis of triazolyl boronates [167].

Furthermore, intramolecular 1,3-dipolar cycloaddition between alkynes **120**, usually obtained as transient intermediates, by treatment of the corresponding aldehydes **121** (derived from α -amino acids) with the Bestmann–Ohira reagent, and an azide leads to series of 1,2,3-triazoles **122** fused with 1,4-benzodiazepines, 1,2,5-benzothiadiazepines, pyrrolobenzodiazepines, and pyrrolobenzothiadiazepines (Scheme 44) [168].

Other methods of triple bond generation for 1,2,3-triazole synthesis were also published. For example, benzotriazoles **123** were prepared by the two-component [169] and three-component [170] classic or microwave-assisted [3 + 2] cycloadditions of sodium azide to benzyne generated from the reaction of an

Scheme 45 Benzotriazoles preparation via MCR**Scheme 46** One-pot Sonogashira coupling-1,3-dipolar cycloaddition reactions

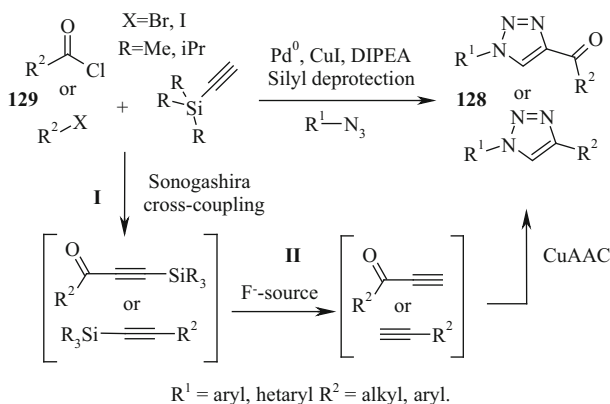
o-(trimethylsilyl)aryl triflate **124** in the presence of arylmethyl halides with either CsF or KF/18-Crown-6. Good to excellent yields of benzotriazoles were obtained in 15–20 min when the microwave-assisted reactions were carried out at 125°C (Scheme 45). These reaction times are significantly faster than similar reactions carried out using conventional heating [170].

4.2 One-Pot Chemical Modification of Alkyne Functional Group Before CuAAC Reaction

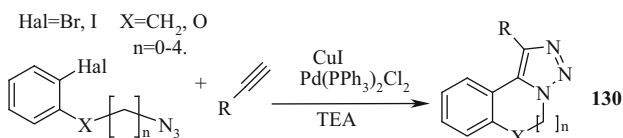
The terminal alkynes, before AAC reaction, may also undergo chemical transformations such as alkylation, arylation, and acylation. This approach allows to functionalize the desired 1,2,3-triazoles in a simple one-pot procedure. For instance, a novel and efficient one-pot way of 4,5-disubstituted-1,2,3-(NH)-triazoles **125** synthesis through palladium-catalysed and ultrasonic promoted Sonogashira coupling/1,3-dipolar cycloaddition of acid chlorides **126**, terminal acetylenes **127**, and sodium azide in one-pot (Scheme 46). The procedure is suitable for many substrates, and various 1,2,3-triazoles can be conveniently produced with excellent yields in a short time using cheap and easily available starting materials [171].

Another example of a one-pot synthetic approach was demonstrated for the synthesis of 1-substituted 4-acyl-1H-1,2,3-triazoles **128** [172, 173]. The reaction involves an initial preparation of TMS-protected or triisopropylsilyl (TIPS)-protected ynones from acid chlorides **129** and TMS or TIPS-acetylene **I**, followed by a TBAF/CuI, CuF₂, or AgF-mediated silanes deprotection **II** and Cu-catalysed Huisgen cycloaddition (Scheme 47). The increased chemical stability of TIPS-protected ynones is an important factor in the high overall product yield [173].

In 2005, the first successful palladium–copper catalysed reaction for the synthesis of fused triazoles **130** was described [174]. The mechanism of the reaction involved the catalytic cycle, which began with the formation of active Pd(0) species accompanied by the formation of an acetylenic dimer. Then coupling through the Sonogashira reaction could lead to the formation of an acyclic precursor, which was



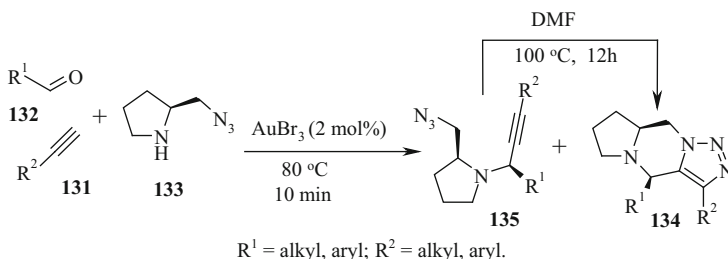
Scheme 47 One-pot three-step synthesis involving cross-coupling-CuAAC processes



Scheme 48 Palladium-copper catalysed reaction for the synthesis of fused triazoles

converted into the cyclic product through IAAC. Recently, a cascade palladium-copper catalysed procedure has been applied for the preparation of fused triazoles by using a bifunctional metal organic framework catalyst containing palladium and copper(II) benzene-1,3,5-tricarboxylate – MOF-Cu (BTC)-[Pd]. This catalyst enables the performance of the tandem Sonogashira/click reaction starting from 2-iodobenzylbromide, sodium azide, and alkynes to produce 8*H*-[1,2,3]triazolo [5,1-*a*]isoindoles with good yields under mild reaction conditions [175]. Moreover, such an approach allows to synthesize 1,2,3-triazoles **130** fused with five-, six-, seven-, and eight-membered benzoheterocycles, including isoindoline, tetrahydroisoquinoline, benzoazepine, and benzoazocine in one-pot as shown in Scheme 48 [176, 177]. The reactions are experimentally simple and utilize easily accessible substrates of different types.

Chen and co-workers attempted to combine, in a one-pot coupling reaction, terminal alkynes **131**, aldehydes **132**, and amines **133** with AAC reaction for the synthesis of several new 4,6,7,8,8*a*,9-hexahydropyrrolo[1,2-*a*][1,2,3]triazolo [1,5-*d*]pyrazines **134** (Scheme 49). The first step involves the AuBr₃-catalysed TCR of terminal alkynes, aldehydes, and amines under solvent-free conditions to provide the requisite propargylamines **135**, which undergo catalyst-free IAAC reactions to give the target triazoles. Unfortunately, in one-pot procedure pyrrolo [1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazine **134** was formed only in very low yields, so it was decided to perform the synthesis in a two-pot protocol, which diastereoselectively gave products in good to excellent yields in short reaction times [178].



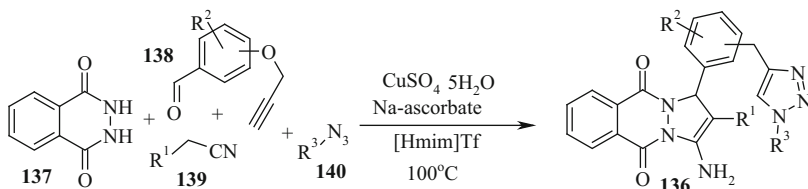
Scheme 49 Synthesis of propargylamines and 4,6,7,8,8a,9-hexahydropyrrolo[1,2-*a*][1,2,3]triazolo[1,5-*d*]pyrazines

4.3 Reaction Between Functional Groups in Substrates Containing Azido and Alkyne Moieties and Subsequent AAC Reaction

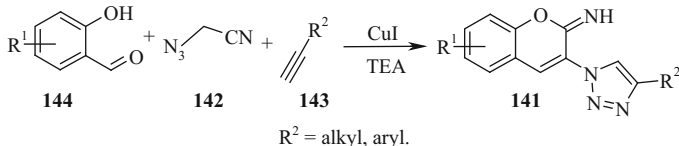
The chemoselectivity of the AAC reaction allows to carry out many parallel reactions, such as alkylation, acylation, and condensation, between a variety of functional groups of substrates containing azido and/or alkyne moieties. For instance, a copper(I)-catalysed 3CR of amines, propargyl halides, and azides forming 1-substituted-1*H*-1,2,3-triazol-4-ylmethyl-dialkylamines in water was demonstrated [179]. Moreover, the application of combined enzyme-metal catalysed methodology allowed to obtain more sophisticated peptides and azides as substrates for the efficient generation of peptidomimetics in a one-pot fashion. For example, CAL-B (*Candida antarctica* lipase B) immobilized on an acrylic resin (Novozyme[®] 435) was found to catalyse the aminolysis of methyl esters with propargyl amine, furnishing propargyl amides which were consecutively transformed into amide ligated 1,2,3-triazoles using CuAAC, in good to excellent yields [180].

A simple and efficient method was proposed for preparation of 1-[(1*H*-1,2,3-triazol-4-yl)methoxy]phenyl-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives **136** in good to excellent yields by a one-pot four-component condensation reaction of phthalohydrazide **137**, a (propargyloxy)benzaldehyde **138**, an active methylene compound **139** (malononitrile or ethyl cyanoacetate), and an azide **140** in the presence of $\text{Cu}(\text{OAc})_2/\text{Na}$ -ascorbate as a catalyst and 1-methyl-1*H*-imidazolium trifluoroacetate ([Hmim]Tf) as an ionic liquid medium (Scheme 50). It is noteworthy that this domino reaction involved the formation of one C–C and four C–N bonds and of two heterocyclic scaffolds in a highly selective manner [181].

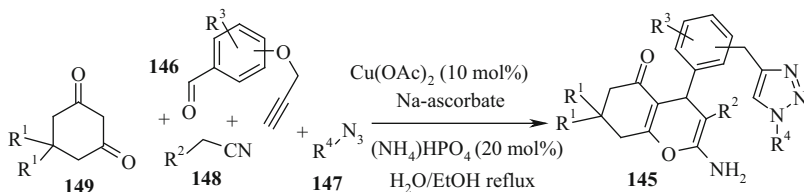
Continuing the above highlighted approach, a variety of 3-triazolyl-2-iminochromenes **141** were synthesized in a one-pot combined Cu(I)-catalysed cycloaddition between 2-azidoacetonitrile **142** and an acetylene **143** forming a triazole and the activated neighbouring methylene group, inducing an aldol-cyclization-dehydration sequence in the presence of a salicylaldehyde **144** (Scheme 51) [182].



Scheme 50 One-pot four-component synthesis of 1-[(triazolylmethoxy)phenyl]-1H-pyrazolo [1,2-*b*]-phthalazine-5,10-diones



Scheme 51 One-pot synthesis of 3-triazolyl-2-iminochromenes

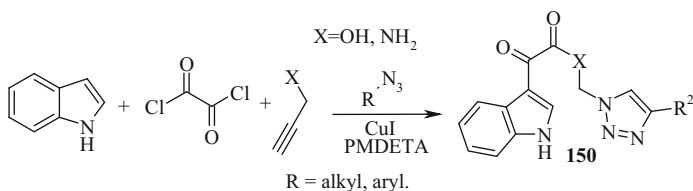
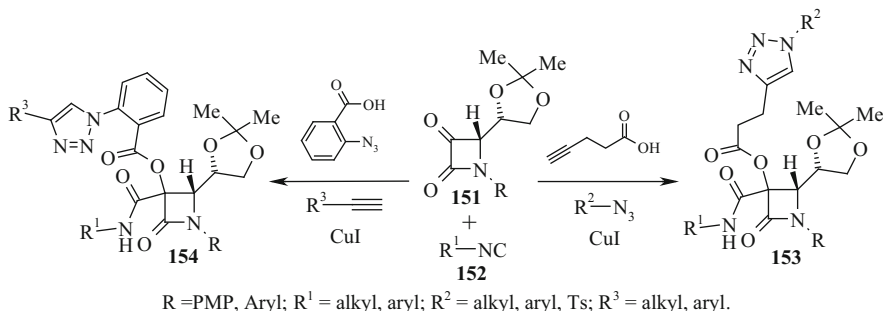


Scheme 52 One-pot synthesis of (1,2,3-triazolyl) methoxyphenyl tetrahydro-5-oxo-4H-chromene

Furthermore, a one-pot procedure was described for the synthesis of (1,2,3-triazolyl) methoxyphenyl tetrahydro-5-oxo-4H-chromene derivatives **145** by concurrent reaction of aryloxy propargylated aldehydes **146**, various azides **147**, active methylene compounds **148**, and 1,3-cyclohexanediones **149** using catalytic amounts of $\text{Cu}(\text{OAc})_2$ /sodium ascorbate and diammonium hydrogen phosphate in aqueous ethanol media (Scheme 52) [183].

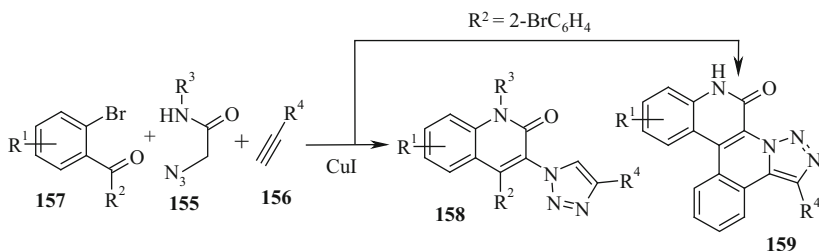
Stefani and co-workers developed a method for the synthesis of indole-3-glyoxyl-1,2,3-triazole derivatives **150** in a one-pot procedure shown in Scheme 53. Typically, the reactions were carried out in dry tetrahydrofuran by mixing indole, oxalyl chloride, a propargyl alcohol or amine and DIPEA at room temperature. Subsequent addition of organic azide, CuI, and PMDETA led to the formation of triazoles **150** [184].

During the last years, the application of the Passerini (P-3CR) and Passerini-Smiles reactions combined with CuAAC has drawn attention as a promising approach for the creation of combinatorial libraries for drug searching. Alcaide and co-workers demonstrated that the Passerini reaction could be coupled with CuAAC using the corresponding alkynes and azides to afford a family of mono-, bis-, and

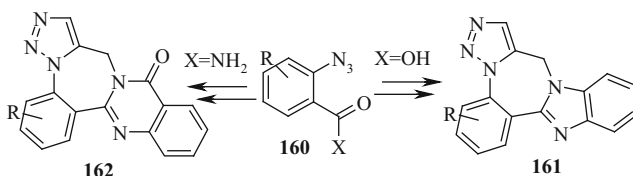
**Scheme 53** One-pot multicomponent synthesis of indole-3-glyoxyl triazoles**Scheme 54** Tandem Passerini-Smiles CuAAC reactions

tris(β -lactam-triazole) hybrids regioselectively. For both one-pot reactions Cu(I) salts were used under anhydrous conditions. For example, the treatment of azetidine-2,3-dione (+) **151** and isocyanide **152**, with 4-pentynoic acid and azides or 2-azido-benzoic acid with alkynes under CuI catalyst and 2,6-lutidine as base at room temperature afforded the corresponding β -lactam triazoles **153**, **154** in moderate to excellent yields (Scheme 54) [185].

Recently, a one-pot domino sequence azide-alkyne cycloaddition, a Goldberg amidation, Camps cyclization, and C-H arylation have been performed for rapid construction of complex heterocycles from three simple components under mild conditions. The proposed possible reaction steps included a CuAAC between a 2-azidoacetamide **155** and acetylene **156** leading to a triazole, in which the adjacent methylene group was activated. Then, in the presence of an *ortho*-carbonyl-substituted aryl halide **157**, the same catalytic system should enable an intramolecular Goldberg amidation, followed by the Camps cyclization (intramolecular aldol-dehydration sequence) to form the 2-quinolinone ring **158**. In case of more reactive electrophiles, such as 2-bromobenzaldehyde, an alternative sequence involving the Knoevenagel condensation followed by intramolecular N-arylation is also possible and leads to the same product **158**. When the R^2 substituent in **157** is the 2-bromoaryl group, a domino sequence should continue to evolve, as the triazolyl group is now perfectly positioned for an intramolecular copper-mediated C-H arylation to afford a pentacycle **159** (Scheme 55) [186].



Scheme 55 One-pot domino sequence AAC, Goldberg amidation, Camps cyclization, and C–H arylation



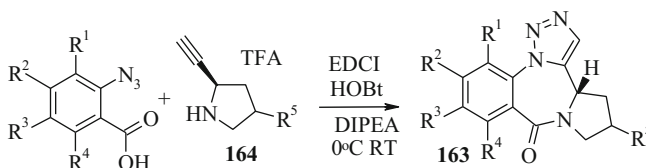
Scheme 56 Synthesis of polycyclic triazoles fused with the benzimidazole and quinazoline ring

4.4 Reaction Between Functional Groups in Substrates Containing Azido and Alkyne Moieties and Subsequent AAC Reaction Leading to the Formation of Polycyclic Compounds with the Fused Triazole Ring

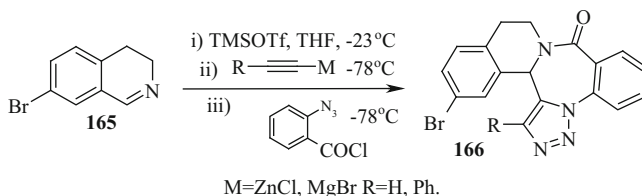
In this section, we focus on the class of reactions leading to the formation of the fused triazoles with unique structures. Typically, these reactions provide new heterocyclic systems, which are difficult or impossible to obtain by other methods or in multi-step manner.

One of the most convenient reagents for these reactions is *ortho*-substituted aromatic azides. For instance, at the end of the eighties of the last century Mohiuddin et al. suggested to use 2-azidobenzoic acid derivatives **160** for the synthesis of polycyclic triazoles fused with the benzimidazole **161** and quinazoline ring **162** in a simple way (Scheme 56) [187, 188].

Since then tandem reaction of *ortho*-substituted carboxylic azides became a very popular and effective strategy. For example, a one-pot synthesis of [1,2,3]triazolo [1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones was described starting from readily available anthranilic acids. The reaction involved amide bond formation employing polymer supported carbodiimide and subsequent 1,3-dipolar cycloaddition reaction. In addition, a number of reagents were tested to activate the *ortho*-azido benzoic acids towards amide bond formation using conventional solution phase methods (DCCI, EDCI, HOBt, etc.), but it was found that in none of the cases the desired adduct was isolated in pure form. In most instances only traces of the



Scheme 57 One-pot amide coupling and IAAC under catalyst-free conditions

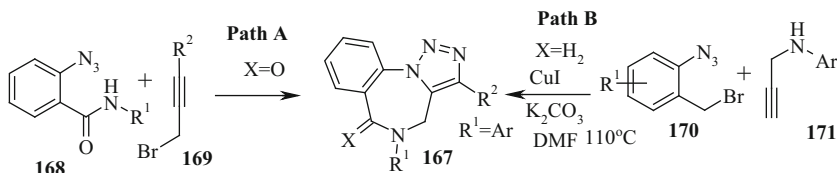


Scheme 58 One-pot synthesis of triazole scaffolds bearing the tetrahydroisoquinoline core

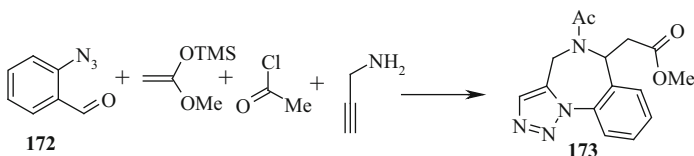
dipolar cycloaddition products were found, even after using excess amine and elevated temperatures [189]. Another example, demonstrated by Molteni et al., is the reaction between 2-methoxycarbonyl-3-thenylazide (3) and propargylamine, which led to the thieno[2,3-*f*][1,2,3]triazolo[1,5-*a*][1,4]diazepine derivative in 25% yield [190]. Using cyclic amines, a one-pot synthesis of novel tetracyclic scaffolds, which incorporate a fusion of a proline, the 1,2,3-triazole ring with the [1,4]-benzodiazepin-8(4H)-one ring systems, was elaborated (Scheme 57). The key step of the reaction is the peptide bond formation followed by in situ 1,3-dipolar cycloaddition in the absence of any catalyst to form triazole **163**. Coupling between aromatic azido acid **160** and TFA salt of amine **164** was carried out in the presence of EDCI, HOBT, and DIPEA in dry DMF. These triazole compounds have been analysed for their efficacy as enzymatic protease inhibitors like serine protease, cysteine protease, and aspartase protease [191].

A novel multicomponent process was developed for the assembly of triazole scaffolds bearing the tetrahydroisoquinoline core. Isoquinolines **165** were allowed to react with either zinc phenylacetylide or ethynylmagnesium bromide in the presence of TMSOTf (Scheme 58) and then trapped with *o*-azidobenzoyl chloride. At room temperature, the amide thus produced readily underwent a dipolar cycloaddition to furnish the novel triazolo-1,5-benzodiazepin-2-ones **166** in 80–93% yields [192].

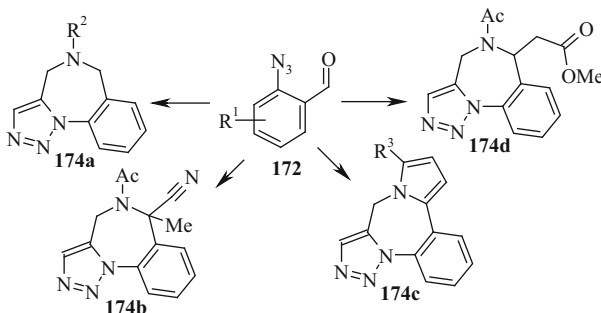
As shown above, intramolecular AAC reaction often takes place regioselectively without the use of a catalyst. Majumdar et al. reported a catalyst-free, one-pot strategy for the synthesis of 1,2,3-triazole-fused 1,4-benzodiazepinone derivatives **167** in good to excellent yields from *N*-substituted 2-azidobenzamides **168** and propargyl bromide **169**, in the presence of base, via *N*-alkylation followed by a 1,3-dipolar cycloaddition (Scheme 59, Path A) [193]. The current approach was modified by the use of *o*-azidobenzylbromide **170** and *N*-propargylated aniline



Scheme 59 Domino strategies for the synthesis of 1,2,3-triazole-fused 1,4-benzodiazepinones



Scheme 60 Tandem MCR/AAC procedure

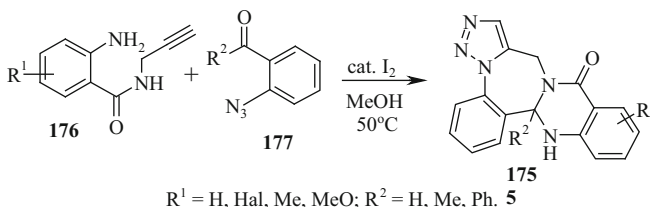
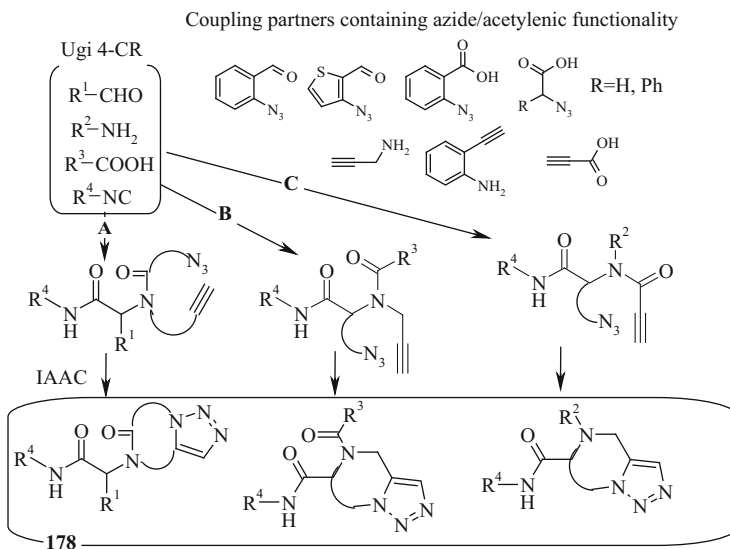


Scheme 61 Synthesis and diversification of 1,2,3-triazole-fused 1,4-benzodiazepines

derivatives **171** in the presence of CuI and base. According to this strategy, triazolo [1,5-*a*][1,4]benzodiazepines **167** with methylene instead of the carbonyl group were prepared (Scheme 59, Path B) [194].

Replacement of the carboxyl group by an aldehyde functionality, in *ortho*-substituted aromatic azides, has provided a new design of domino reactions. Thus, cascade reactions were constructed involving condensation of 2-azidobenzaldehyde **172** with propargyl amine furnishing an imine that was treated with acetyl chloride and a ketene acetal to furnish the triazole **173** via a [3 + 2] dipolar cycloaddition (Scheme 60). The key element of the strategy is a one-pot process incorporating four components [195].

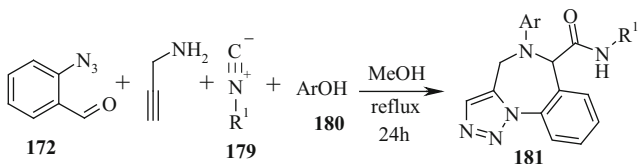
Recently, a substituted heterocyclic scaffold, comprising a 1,4-benzodiazepine fused with a 1,2,3-triazole ring **174a–d**, was synthesized from 2-azidobenzaldehyde **172** employing a reductive amination or amination combined with nucleophilic addition, followed by a thermally induced, intramolecular Huisgen cycloaddition (Scheme 61) [196]. Furthermore, it was shown that this strategy was suitable for the

**Scheme 62** One-pot two-step cascade synthesis of quinazolinotriazolobenzodiazepines**Scheme 63** Fused triazole derivatives by the sequential Ugi and IAAC

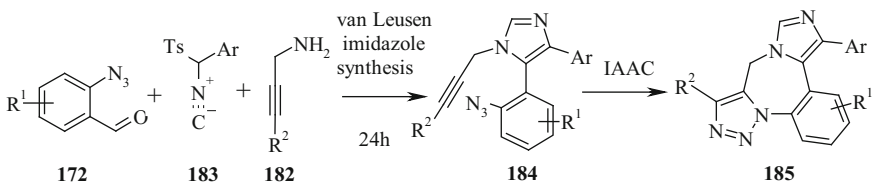
preparation of diverse libraries of compounds, tested in a wide range of biological assays [197].

A one-pot two-step cascade method was developed to afford quinazolino[1,2,3]triazolo[1,4]benzodiazepines **175** via sequential quinazolinone-forming condensation and IAAC reactions. Step one consists of an anilino-keto condensation to form a Schiff base and subsequent nucleophilic attack by the amide nitrogen onto the imine to form an amina (quinazolinone). These two iodine-promoted condensations preorganize the alkyne (from **176**) and azide (from **177**) groups for an intramolecular 1,3-dipolar cycloaddition (step two) to form a complex pentacyclic system (Scheme 62) [198].

Akritopoulou-Zanze and co-workers elaborated the facile construction of fused triazole derivatives **178** by a sequential Ugi and IAAC. The synthetic sequence is described in Scheme 63. A variety of six- and seven-membered ring systems fused to triazoles have been synthesized as the authors successfully used coupling partners containing an azide functionality on the carboxylic acid (Route A) or aldehyde



Scheme 64 Tandem four-component Ugi-Smiles-type AAC reactions



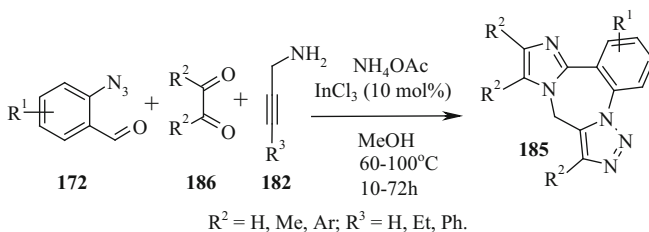
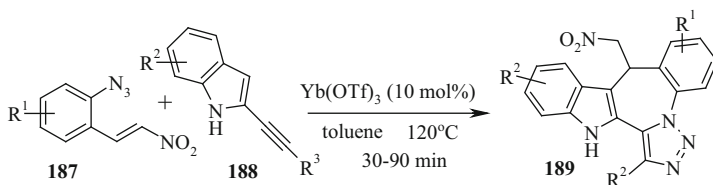
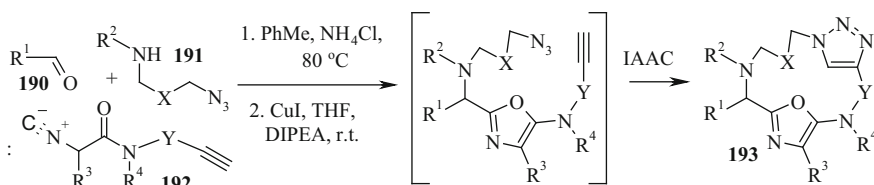
Scheme 65 Sequential van Leusen/alkyne-azide cycloaddition reactions

inputs (Routes B and C) and acetylenic functionalities on the amine (Routes A and B) or carboxylic acid (Route C) inputs [199].

Moreover, it was shown that the use of 2-azidobenzaldehyde **172** and propargylamine in a Ugi-Smiles coupling gave an easy access to 4,5-dihydro-1,2,3-triazolo[1,5-*a*][1,4]benzodiazepine derivatives **181**. The approach is based on the reaction between 2-azidobenzaldehyde, propargylamine, isocyanides **179**, and nitrophenols **180** in methanol under reflux conditions without using additional reagents or catalysts (Scheme 64). In addition, two possible reaction mechanisms were proposed. The first mechanism supposes that the formation of Ugi adduct takes place before AAC; while according to the second mechanism, the cyclization reaction and the formation of the benzodiazepine ring are prior to the Ugi reaction [200].

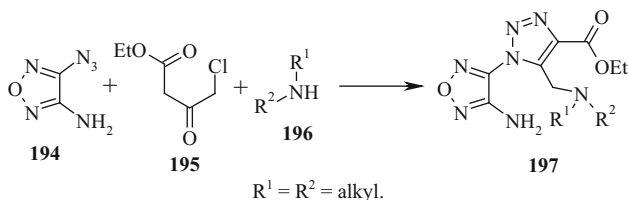
Furthermore, a fused triazolo imidazole derivative synthesis was reported with good overall yields by a van Leusen/alkyne-azide cycloaddition synthetic sequence from simple starting materials in an expedient fashion (Scheme 65). The use of azide **172** containing the aldehyde moiety, alkyne **182** containing the amine, and isocyanide **183** resulted in a four-component Ugi-Smiles-type reaction providing the intermediate for the van Leusen reaction which led to substrate **184**. Subsequent cyclization via the IAAC allows access to the fused triazolo imidazole scaffolds **185** [201].

Another example of a fused imidazotriazolobenzodiazepines derivatives **185** synthesis was demonstrated via the transformation, incorporating α -diketones **186**, o-azidobenzaldehydes **172**, propargylic amines **182**, and ammonium acetate via indium(III)-catalysed reaction (Scheme 66). This process involves tandem InCl_3 -catalysed cyclocondensation and IAAC reaction. A series of transition metal Lewis acids [$\text{Cu}(\text{OAc})_2$, FeCl_3 , $\text{Zn}(\text{ClO}_4)_2$, $\text{Sc}(\text{OTf})_3$, CeCl_3 , InCl_3 , InBr_3] were examined for their ability to activate 1,2-dicarbonyl electrophiles **186** [202].

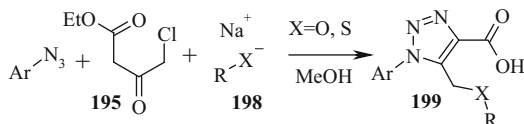
**Scheme 66** Imidazotriazolobenzodiazepines via indium(III)-catalysed MCRs**Scheme 67** Cascade Michael addition-IAAC reactions**Scheme 68** One-pot synthesis of macrocycles by a three-component reaction/[3 + 2] cycloaddition

Moreover, the 2-nitrovinyl moiety (compound **187**) was used as synthetic equivalent of the aldehyde group. Such a replacement allows to synthesize indole-based polyheterocycles via a sequential Lewis acid catalysed Michael addition and an IAAC reaction. As a result of such a strategy, tetracyclic indolo[2,3-*c*][1,2,3]triazolo[1,5-*a*][1]benzazepines **189** were synthesized in good yields under mild reaction conditions from indole **188** in a one-pot reaction (Scheme 67) [203].

In addition, a straightforward synthesis of complex macrocycles was described from readily accessible starting materials by a tandem process involving a three-component reaction between an aldehyde **190**, an ω -azido amine **191**, and an isocynoacetamide **192** and subsequent IAAC, which led to macrocyclic 1,2,3-triazoles **192** in good yields (Scheme 68) [204].



Scheme 69 N-nucleophiles in subsequent SN-azides cyclocondensation reactions



Scheme 70 S-, O-nucleophiles in subsequent SN-azides cyclocondensation reactions

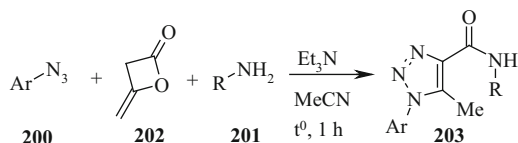
5 One-Pot Multi-Step Triazole Synthesis Involving Azide Reactions with Activated Acetonitriles or Ketomethylene Compounds and Subsequent Triazole Function Group Transformation

The reactions of azides with active methylene reagents are less studied than the AAC, but they also were amenable to multicomponent strategies. For instance, the 1-(4-aminofurazan-3-yl)-5-dialkylaminomethyl-1*H*-[1,2,3]triazole-4-carboxylic acids **197** were prepared by a one-pot procedure using 3-azido-2-amino-1,2,5-oxadiazole **194**, ethyl chloroacetoacetic acid **195** and an excess of the appropriate amines **196** (Scheme 69) and tested in a GSK-3 inhibition assay [205].

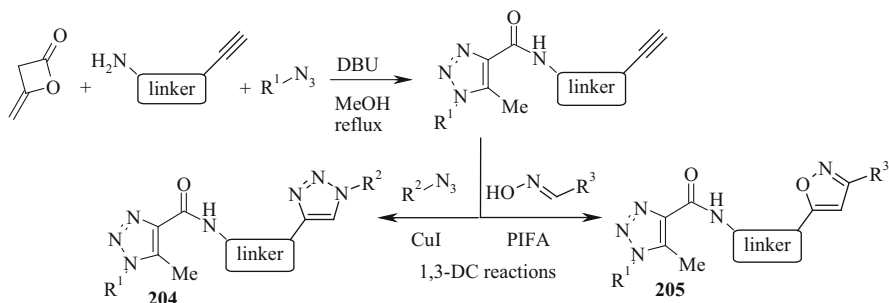
For diversification of such a strategy, O- or S-nucleophiles **198** were used and the optimization of reaction conditions led to substituted 1*H*-1,2,3-triazole-4-carboxylic acids **199**. The reaction of azide with **195** and O-nucleophile (methylate anion) was carried out under strict control of temperature to avoid undesirable reactions, and yields of triazoles **199** were moderate (Scheme 70) [206].

In 2009, Pokhodylo and co-workers elaborated a convenient synthetic protocol for the creation of combinatorial libraries of 1-(R^1 -phenyl)-5-methyl-*N*- R^2 -1*H*-1,2,3-triazole-4-carboxamides **203** from commercially available or readily prepared azides **200**, amines **201**, and diketene **202**. It was noted that the reaction of diketene with highly nucleophilic amines and reactive azides proceeded at room temperature, and the yields of the reaction increased with an increase of amine basicity (Scheme 71) [207].

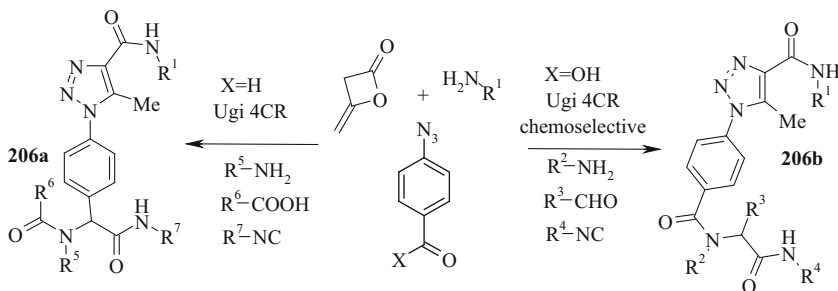
Recently, this strategy has been combined with 1,3-dipolar cycloaddition to an efficient chemoselective methodology for the syntheses of unsymmetrical bis (1,2,3-triazole) (**204**) [208] and isoxazole (**205**) [209] derivatives (Scheme 72). This protocol utilizes alkynyl-substituted amines as bifunctional linkers to conjoin a



Scheme 71 One-pot multicomponent synthesis of 1-aryl-5-methyl-*N*-R²-1*H*-1,2,3-triazole-4-carboxamides



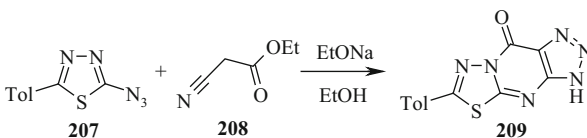
Scheme 72 Chemoselective preparation of 1,2,3-triazole-triazole/isoxazole peptidomimetics



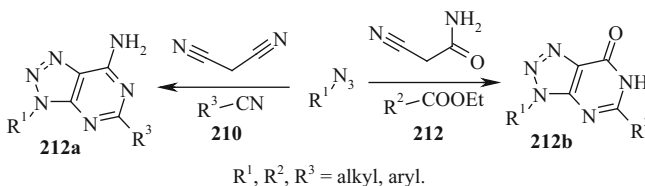
Scheme 73 The 3CR synthesis of 5-methyl-1*H*-1,2,3-triazoles combined with Ugi four-component reaction

copper-free three-component cycloaddition with a cycloaddition in a one-pot procedure. In particular, this methodology is suitable for the synthesis of unsymmetrical bisfunctional-modified peptidomimetics by the combination of MCRs in a sequential process, which allows direct access to complex structures from simple building blocks.

Furthermore, the protocol for a three-component synthesis of 5-methyl-1*H*-1,2,3-triazoles was combined with the Ugi four-component reaction, which allowed to construct diversified 5-methyl-1*H*-1,2,3-triazole modified peptidomimetics **206a,b**. The protocol can be useful in biochemistry and medicinal discovery (Scheme 73) [210].



Scheme 74 Domino transformation leading to [1,3,4]thiadiazolo[3,2-a][1,2,3]triazolo[4,5-d]pyrimidine



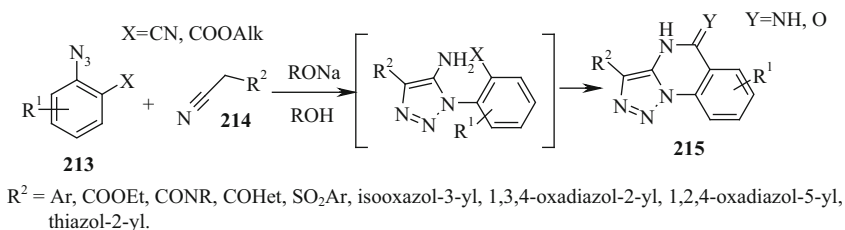
Scheme 75 Subsequent triazole formation and pyrimidine ring annulation

Base catalysed azide reactions with activated acetonitrile occur quite rapidly, allowing to obtain triazoles with a functional group capable for subsequent one-pot domino transformations. For example, 6-(4-methylphenyl)-[1,3,4]thiadiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]pyrimidin-9(1*H*)-one **209** was prepared from 2-azido-5-(4-methylphenyl)-1,3,4-thiadiazole **207**, ethyl cyanoacetate **208** and sodium ethoxide as a catalyst (Scheme 74). The reaction involves triazole formation, the Dimroth rearrangement, and thiadiazole acylation by the carboxylic group [211].

Another multicomponent methodology was elaborated for the synthesis of azapurine-related compounds **212** starting from azides, malononitrile or cyanacetic derivatives and an aliphatic or aromatic nitrile **210** or ester **211**. The approach involves the formation of a triazole containing amino and either a carbonyl, amide or nitrile group that undergo the following tandem transformation to annulated pyrimidines (Scheme 75) [212–220].

6 Domino Reactions of *Ortho*-Substituted Azides with Active Methylene Compounds

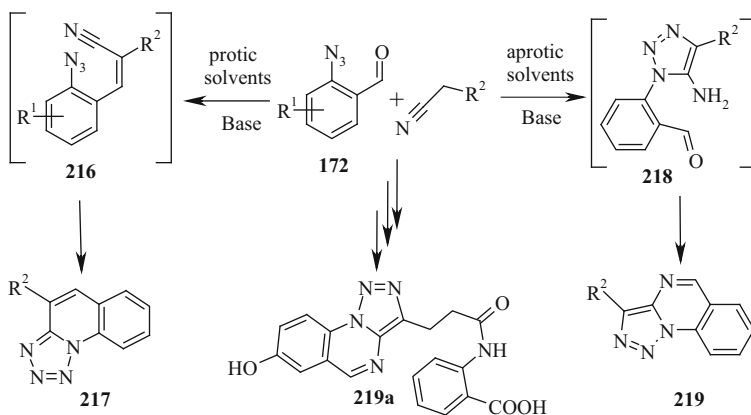
The reactions of *ortho*-substituted aromatic azides with activated acetonitrile were the first examples of domino strategies, which led to 1,2,3-triazole preparation. In 1966, G. Tennant showed that *o*-azidobenzoic acid **213a** condensed with phenylacetonitrile **214a** in methanolic sodium methoxide to give 4,5-dihydro-5-oxo-3-phenyl-1,2,3-triazolo[1,5-*a*]quinazoline **215** (Scheme 76) [221]. This work has inspired a series of similar transformations, which allowed obtaining new complex fused heterocyclic systems with various substituents for the study of their properties. For



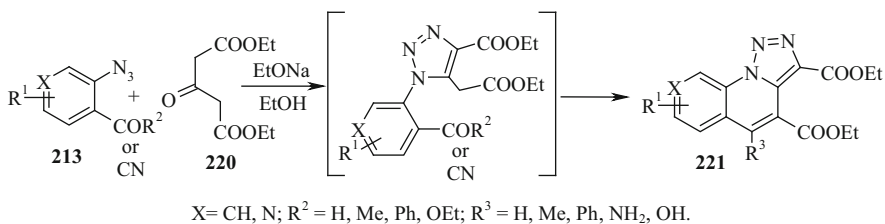
Scheme 76 Domino reactions of *ortho*-CN or COOR aryl azides with activated acetonitrile

instance, such a base-catalysed condensation of the substituted *o*-azidobenzonitrile **213b** was studied with active methylene compounds containing a cyanogroup, such as arylacetonitrile, arylsulphonylacetonitriles, cyanoacetic acid, ethyl cyanoacetate, cyanoacetamide, and malononitrile, giving high yields of triazolo[1,5-*a*]quinazolines **215** (Scheme 76) [222–224]. Moreover, novel 3-substituted-1,2,3-triazolo[1,5-*a*]quinazolinones **215** were synthesized in high yields via anionic domino reaction with acetonitriles activated by the thiazole, benzothiazole, 1,3,4-oxadiazole, and 1,2,4-oxadiazole rings. It was shown that acetonitriles exhibited high reactivity and were convenient methylenic compounds for such reactions providing rapid structural variation [225–227]. Further applications of such reactions included the reaction of the homolog of amino benzoic ester, leading to the formation of 4*H*-[1,2,3]triazolo[1,5-*a*]-[1,3]benzodiazepin-5(6*H*)-ones [228]. Recently, some 3-ethoxycarbonyl or 3-phenyl-substituted 1,2,3-triazolo[1,5-*a*]quinazolines have been synthesized using domino reaction as a key step, and the biological affinity towards benzodiazepine and A1 and A2A adenosine receptors was evaluated [229]. 3-Arylsulphonyl-[1,2,3]triazolo[1,5-*a*]quinazolines were synthesized as targocil analogues and tested as Wall Teichoic Acid biosynthesis inhibitors [230, 231]. Additionally, a combinatorial library consisting of the substituted 3-phenylsulphonyl-[1,2,3]triazolo[1,5-*a*]quinazolines was created and a study of the relation of their structure with 5-HT6 receptor antagonistic activity was undertaken [232].

When replacing the carboxyl group at the aldehyde moiety in starting azide component the possibility of alternative Knoevenagel condensation appears instead of 1,2,3-triazolo[1,5-*a*]quinazoline formation. However, condensation of malononitrile with 2-azidobenzaldehyde **172** yielded cyano-1,2,3-triazolo[1,5-*a*]quinazoline **219** or tetrazolo[1,5-*a*]quinoline **217** depending on the base and reaction conditions. In protic solvents, 2-azidobenzaldehyde **172** undergoes a base-catalysed condensation with cyanide-stabilized carbanions to generate the corresponding intermediate **216**, which then forms tetrazolo[1,5-*a*]quinolines **217**, whereas in aprotic media intermediate **218** leads to 1,2,3-triazolo[1,5-*a*]quinazolines **219** (Scheme 77). The attack of cyanide-stabilized carbanions on azide functions led to the formation of 1,2,3-triazole **219** [233]. This approach was used for the preparation of tricyclic agonists **219a** for the high affinity niacin receptor G-protein-coupled receptor (GPR) 109A [234, 235]. The use of *ortho*-keto azides in domino reactions also was studied in several reports. For example, regioselective attack of cyanide-stabilized carbanions at the azide instead of carbonyl group of



Scheme 77 Aromatic *ortho*-aldehyde azides in domino reaction



Scheme 78 Domino reaction of 1,3-acetonedicarboxylate with *ortho*-substituted azides

2'-azidoacetophenone led to the formation of 5-methyltriazolo[1,5-*a*]quinazolines [233]. Recently, synthesis and purification of aryl azides were reported to be incorporated into a multistep flow sequence to generate triazolo[1,5-*a*]quinazoline directly from aniline starting materials in a fully automated fashion [236].

Smalley and Teguche reported the preparation of 1,2,3-triazolo[1,5-*a*]quinoline-4,5-dicarboxylates **221** by the action of the diethyl 1,3-acetonedicarboxylate **220** anion on *ortho*-substituted aryl azides *o*-azidoacetophenones, *o*-azidobenzaldehyde **172** and methyl *o*-azidobenzoate **213a**. The anion was formed using either sodium alkoxide in the appropriate alcohol or by an ion-exchange resin [Amberlite IRA-400 (OH)]. Furthermore, the authors demonstrated application of heterocyclic azides. It was found out that 3-azido-4-cyanopyridine **213b** and ethyl 3-azidopyridine-4-carboxylate **213c** behaved similarly with activated acetonitriles to produce the amino/oxy-1,2,3-triazolo[1,5-*a*][1,7]naphthyridine **221** respectively (Scheme 78) [237].

Westerlund reported the first synthesis of a new system 1,2,3-triazolo[1,5-*a*]thieno[3,2-*d*]pyrimidine **222** by the reaction of active methylene nitriles with 3-azido-2-substituted thiophenes [238]. Recently, thienopyridines have been prepared from 3-cyanopyridine. An anionic domino reaction with nitriles, possessing an active methylene group, gave a new polycyclic system. The reaction takes only a few minutes and products are obtained in high yields after crystallization from the reaction mixture without further purification. This approach allows the synthesis of

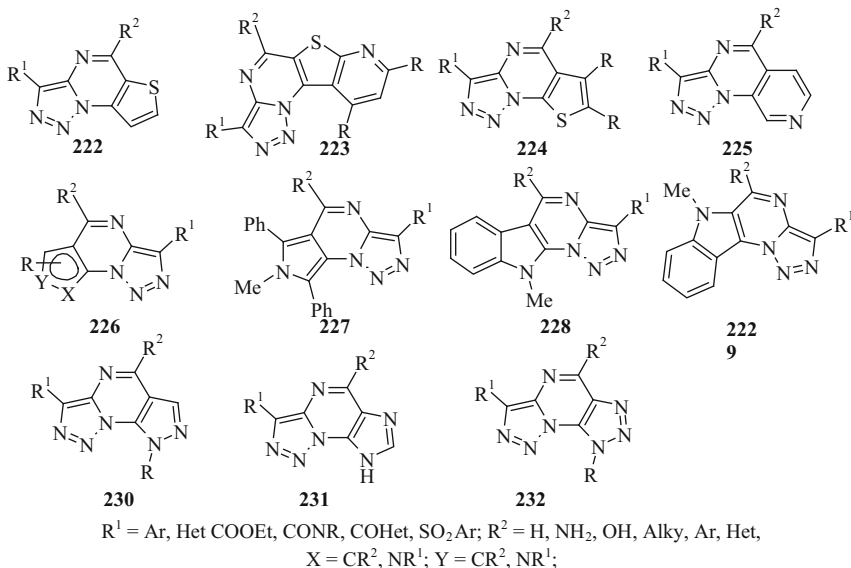
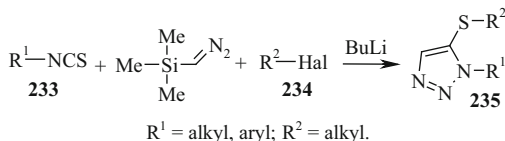


Fig. 3 Heterocyclic [1,2,3]triazolo[1,5-a]pyrimidine via domino reaction

derivatives of the new heterocyclic system pyrido[3',2':4,5]thieno[2,3-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine **223** [239]. Such heterocyclic systems became main scaffolds for evaluation of biological activity and a domino reaction is generally used for the creation of the corresponding compounds libraries. For instance, representatives of thieno[3,2-*d*][1,2,3]triazolo[1,5-*a*]pyrimidine **222** were selected for anti-cancer screening against a panel of 60 human tumour cell lines [240]. A number of 3-(phenylsulphonyl)thieno[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidines were prepared and their 5-HT₆ receptor binding affinity and ability to inhibit the functional cellular responses to serotonin were evaluated [241]. Furthermore, by high-throughput screening, a triazolothienopyrimidine UT-B inhibitor that selectively and reversibly inhibited urea transport with IC₅₀ = 25.1 nM and reduced urinary concentration in mice was identified [242]. In addition, a novel class of triazolothienopyrimidine (TTPM) compounds was identified as potent HIV-1 replication inhibitors during a high-throughput screening campaign that evaluated more than 200,000 compounds using a cell-based full replication assay [243]. Pokhodylo and co-workers reported the synthesis of derivatives of a new ring system thieno[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **224** in high yields via an anionic hetero-domino reaction. It was found out that 2-azidothiophenes reacted with acetonitriles in sodium methoxide methanol solution with appreciable exothermal effect and the reaction was completed within 1–2 min. Notably in general the product of the reaction was formed immediately after mixing the reagents except for phenylacetoneitrile, which reacted slower [244]. This method is not working for shielded carbonyl starting materials. In this case, reaction stopped at the formation of the intermediate aminotriazole, instead going to the expected thieno[3,2-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine (Fig. 3) [245].

Scheme 79 Non-azidic multicomponent triazole synthesis



Lauria and co-workers have reported several examples of the use of these domino reactions to obtain five-membered nitrogen heterocycles. Firstly, derivatives of the new ring system pyrrolo[3,4-*e*][1,2,3] triazolo[1,5-*a*]pyrimidine **226**, **227** were prepared in high yields by a one-step reaction of azidopyrrole and substituted acetonitriles [246, 247]. Then the derivatives of the new ring system indolo[3,2-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine **228** were easily prepared from 2-azidoindole. It was the first example of an anionic domino reaction in the indole series [248]. Later, indolo[2,3-*e*][1,2,3]triazolo[1,5-*a*]pyrimidine derivatives **229** were obtained from 3-azidoindoles. It was also noted that all the fused [1,2,3] triazolo[1,5-*a*]pyrimidines can be used as models for the design of DNA-interactive compounds [249, 250]. The reaction is used for pyrazole **230**, imidazole **231**, and triazole **232** azides leading to pyrazolo[3,4-*d*][1,2,3]triazolo[1,5-*a*]pyrimidines [251, 252], 8*H*-[1,2,3]triazolo[5,1-*b*]purines [253] and triazolo[4,3-*e*]-*v*-triazolo[1,5-*a*]pyrimidines [254–256].

7 Non-Azidic Multicomponent Triazole Synthesis

In this final section attention is drawn to the fact that not only azides may be precursors in the synthesis of triazoles **235** via multicomponent strategies. Unfortunately, alternative reactions are less studied, since in many cases the use of azides is favourable due to the high accessibility. However, attention may be given to trimethylsilyldiazomethane as triazole precursor. In several reports, one-pot synthesis of 1-substituted-5-alkylthio-1,2,3-triazoles was demonstrated by the treatment of isothiocyanates **233** with lithium trimethylsilyldiazomethane, prepared from TMSCHN₂ and *n*-butyllithium, followed by quenching with alkyl halides **234** (Scheme 79) [257–260].

8 Conclusion

From the reviewed reports it appears obvious that the high rate of azide reactions with alkynes, as well as with methylene active compounds, in combination with a high chemoselectivity of these reactions, makes it possible to combine them with a variety of organic reactions in a one-pot procedure to provide multicomponent domino reactions. By such reactions, the preparation of 1,2,3-triazoles with unique structure, valuable properties in a convenient, economical, and safe way is possible.

9 Addendum

This review covered the field up to November 30, 2013.

References

1. Orru RVA, Ruijter E (eds) (2010) Synthesis of heterocycles via multicomponent I. Top Heterocycl Chem 23:1–280
2. Orru RVA, Ruijter E (eds) (2010) Synthesis of heterocycles via multicomponent II. Top Heterocycl Chem 25:1–292
3. Zhu J, Bienaymé H (eds) (2010) Multicomponent reactions, 1st edn. Wiley-VCH, Weinheim, pp 1–468
4. Müller TJJ (2011) Beilstein J Org Chem 7:960
5. Nicolaou KC, Edmonds DJ, Bulger PG (2005) Angew Chem Int Ed 45:7134
6. Dömling A, Ugi I (2000) Angew Chem Int Ed 39:3168
7. Tietze LF, Brasche G, Gericke K (2006) Domino reactions in organic synthesis. Wiley-VCH, Weinheim, pp 1–672
8. Pellissier H (2006) Tetrahedron 62:1619
9. Pellissier H (2006) Tetrahedron 62:2143
10. Tietze LF (1996) Chem Rev 96:115
11. Bunce RA (1995) Tetrahedron 51:13103
12. Tietze LF, Beifuss U (1993) Angew Chem Int Ed 32:131
13. Ho TL (1992) Tandem organic reactions. Wiley, New York, pp 1–502
14. Matlack AS (2001) Introduction to green chemistry. Marcel Dekker, New York, pp 1–570
15. Anastas PT, Warner JC (2000) Green chemistry: theory and practice. Oxford University Press, Oxford, pp 1–135
16. Kolb HC, Finn MG, Sharpless KB (2001) Angew Chem Int Ed 40:2004
17. Thirumurugan P, Matosiuk D, Jozwiak K (2013) Chem Rev 113:4905
18. Wong C-H, Zimmerman SC (2013) Chem Commun 49:1679
19. Janez K (ed) (2012) Click triazoles. Top Heterocycl Chem 28:1–236
20. Palomo JM (2012) Org Biomol Chem 10:9309
21. Finn MG, Fokin V (eds) (2010) Themed issue: applications of click chemistry. Chem Soc Rev 39:1223–1407
22. Amblard F, Cho JH, Schinazi RF (2009) Chem Rev 109:4207
23. Meldal M, Tornøe CW (2008) Chem Rev 108:2952
24. Tron GC, Pirali T, Billington RA, Canonico PL, Sorba G, Genazzani AA (2008) Med Res Rev 28:278
25. Angell YL, Burgess K (2007) Chem Soc Rev 36:1674
26. Gil MV, Arévalo MJ, López Ó (2007) Synthesis 1589
27. Bock VD, Hiemstra H, van Maarseveen JH (2006) Eur J Org Chem 51
28. Wu Y-M, Deng J, Li Y, Chen Q-Y (2005) Synthesis 1314
29. Wu Y-M, Deng J, Chen Q-Y (2006) Synlett 645
30. Yoo EJ, Ahlquist M, Bae I, Sharpless KB, Fokin VV, Chang S (2008) J Org Chem 73:5520
31. Abbott Laboratories (2008) WO 154241
32. Martin SW, Bergstrom CP, Gentles RG, Yeung K-S (2010) WO 93359
33. Carcenac Y, Abarbri M, Duchene A, Thibonnet J, David-Quillot F (2013) Synthesis 633
34. Diner P, Andersson T, Kjellen J, Elbing K, Hohmann S, Groetli M (2009) New J Chem 33:1010
35. Li N, Zhang G, Zhu A, Zhang L (2008) J Org Chem 73:3630

36. Hein JE, Tripp JC, Krasnova LB, Sharpless KB, Fokin VV (2009) *Angew Chem Int Ed* 48:8018
37. Hein JE, Tripp JC, Krasnova L, Sharpless KB, Fokin VV (2011) *WO* 19799
38. Worrell BT, Hein JE, Fokin VV (2012) *Angew Chem Int Ed* 51:11791
39. Smith NW, Polenz BP, Johnson SB, Dzyuba SV (2010) *Tetrahedron Lett* 51:550
40. Brotherton WS, Clark RJ, Zhu L (2012) *J Org Chem* 77:6443
41. Barsoum DN, Brassard CJ, Deeb JHA, Okashah N, Sreenath K, Simmons JT, Zhu L (2013) *Synthesis* 45:2372
42. Rostovtsev VV, Green LG, Fokin VV, Sharpless KB (2002) *Angew Chem Int Ed* 41:2596
43. Himo F, Lovell T, Hilgraf R, Rostovtsev VV, Noodleman L, Sharpless KB, Fokin VV (2005) *J Am Chem Soc* 127:210
44. Tanaka K, Kageyama C, Fukase K (2007) *Tetrahedron Lett* 48:6475
45. Yan R, Sander K, Galante E, Rajkumar V, Badar A, Robson M, El-Emir E, Lythgoe MF, Pedley RB, Årstad E (2013) *J Am Chem Soc* 135:703
46. Li L, Li Y, Li R, Zhu A, Zhang G (2011) *Aust J Chem* 64:1383
47. Li L, Li R, Zhu A, Zhang G, Zhang L (2011) *Synlett* 874
48. De Simone R, Chini MG, Bruno I, Riccio R, Bifulco G, Mueller D, Werz O (2011) *J Med Chem* 54:1565
49. Goyard D, Praly J-P, Vidal S (2012) *Carbohydr Res* 362:79
50. Zhang X, Hsung RP, Li H (2007) *Chem Commun* 2420
51. Ackermann L, Potukuchi HK, Landsberg D, Vicente R (2008) *Org Lett* 10:3081
52. Alonso F, Moglie Y, Radivoy G, Yus M (2012) *Synlett* 2179
53. Angell Y, Burgess K (2007) *Angew Chem Int Ed Engl* 46:3649
54. Li L, Fan X, Zhang Y, Zhu A, Zhang G (2013) *Tetrahedron* 69:9939
55. Wang B, Ahmed MN, Zhang J, Chen W, Wang X, Hu Y (2013) *Tetrahedron Lett* 54:6097
56. Cai Q, Yan J, Ding K (2012) *Org Lett* 14:3332
57. Malnuit V, Duca M, Manout A, Bougrin K, Benhida R (2009) *Synlett* 2123
58. Li L, Hao G, Zhu A, Fan X, Zhang G, Zhang L (2013) *Chem Eur J* 19:14403
59. Zhou Y, Lecourt T, Micouin L (2010) *Angew Chem Int Ed* 49:2607
60. Akimova GS, Chistokletov VN, Petrov AA (1967) *Zh Org Khim* 3:968
61. Akimova GS, Chistokletov VN, Petrov AA (1967) *Zh Org Khim* 3:2241
62. Akimova GS, Chistokletov VN, Petrov AA (1968) *Zh Org Khim* 4:389
63. Krasinski A, Fokin VV, Sharpless KB (2004) *Org Lett* 6:1237
64. E. I. Du pont de nemours and company (2009) *WO* 137538
65. Meza-Avina ME, Patel MK, Lee CB, Dietz TJ, Croatt MP (2011) *Org Lett* 13:2984
66. Akao A, Tsuritani T, Kii S, Sato K, Nonoyama N, Mase T, Yasuda N (2007) *Synlett* 31
67. Zink DM, Braese S, Baumann T, Nieger M (2011) *Eur J Org Chem* 1432
68. Liu D, Gao W, Dai Q, Zhang X (2005) *Org Lett* 7:4907
69. Dai Q, Gao W, Liu D, Capes LM, Zhang X (2006) *J Org Chem* 71:3928
70. Feldman AK, Colasson B, Fokin VV (2004) *Org Lett* 6:3897
71. Appukkuttan P, Dehaen W, Folkin VV, Van der Eycken E (2004) *Org Lett* 6:4223
72. Kacprzak K (2005) *Synlett* 943
73. Sharpless WD, Wu P, Hansen TV, Lindberg JG (2005) *J Chem Educ* 82:1833
74. Chittaboina S, Xie F, Wang Q (2005) *Tetrahedron Lett* 46:2331
75. Molander GA, Ham I (2006) *J Org Lett* 8:2767
76. Zhang X, Li H, You L, Tang Y, Hsung RP (2006) *Adv Syn Catal* 348:2437
77. Zhang X, Hsung RP, You L (2006) *Org Biomol Chem* 4:2679
78. Pericherla K, Khedar P, Khungar B, Kumar A (2012) *Tetrahedron Lett* 53:6761
79. Odlo K, Hoeydahl EA, Hansen TV (2007) *Tetrahedron Lett* 48:2097
80. Kumar D, Patel G, Reddy VB (2009) *Synlett* 399
81. Sreedhar B, Reddy PS (2007) *Synth Commun* 37:805
82. Sarmiento-Sanchez JI, Ochoa-Teran A, Rivero IA (2011) *ARKIVOC* 2011:177
83. Oezcubukcu S, Ozkal E, Jimeno C, Pericas MA (2009) *Org Lett* 11:4680–4683
84. Wang D, Li N, Zhao M, Shi W, Ma C, Chen B (2010) *Green Chem* 12:2120

85. Lal S, Díez-González S (2011) *J Org Chem* 76:2367
86. Liu M, Reiser O (2011) *Org Lett* 13:1102
87. Garcia-Alvarez J, Díez J, Gimeno J, Suarez FJ, Vincent C (2012) *Eur J Inorg Chem* 5854
88. Zhao Y-B, Yan Z-Y, Liang Y-M (2006) *Tetrahedron Lett* 47:1545
89. Yan J, Wang L (2010) *Synthesis* 447
90. Díez-González S, Correa A, Cavallo L, Nolan SP (2006) *Chem Eur J* 12:7558
91. Liu J, Liu M, Yue Y, Yao M, Zhuo K (2012) *Chin J Chem* 30:644
92. Wang W, Wu J, Xia C, Li F (2011) *Green Chem* 13:3440
93. Wang Y, Liu J, Xia C (2011) *Adv Synth Catal* 353:1534
94. Gu S, Liu X, Liu H, Zhou Y, Huang J, Xu W (2012) *Inorg Chem Commun* 21:168
95. Wan L, Cai C (2012) *Catal Lett* 142:1134
96. Kamata K, Nakagawa Y, Yamaguchi K, Mizuno N (2008) *J Am Chem Soc* 130:15304
97. Yamaguchi K, Kotani M, Kamata K, Mizuno N (2008) *Chem Lett* 37:1258
98. Shamim T, Paul S (2010) *Catal Lett* 136:260
99. Hosseinzadeh R, Shahrokhi F, Sepehrian H (2012) *Heteroatom Chem* 23:415
100. Coelho A, Diz P, Sotelo E, Caamano O (2010) *Adv Synth Catal* 352:1179
101. Kumar BSPA, Reddy KHV, Madhav B, Ramesh K, Nageswar YVD (2012) *Tetrahedron Lett* 53:4595
102. Nasir Baig RB, Varma RS (2013) *Green Chem* 15:398
103. Nador F, Radivoy G, Volpe MA, Alonso F, Feldhoff A, Kirschning A (2013) *Appl Catal A Gen* 455:39
104. Nasir Baig RB, Varma RS (2012) *Green Chem* 14:625
105. Cook TL, Walker JA, Mack J (2013) *Green Chem* 15:617
106. Mukherjee N, Ahammed S, Bhadra S, Ranu BC (2013) *Green Chem* 15:389
107. Alix A, Sido KSS, Pale P, Boningari T, Keller M, Kuhn P, Sommer J, Louis B, Chassaing S (2010) *Synthesis* 1557
108. Beneteau V, Olmos A, Pale P, Boningari T, Sommer J (2010) *Tetrahedron Lett* 51:3673
109. Albadi J, Keshavarz M, Abedini M, Vafaie-Nezhad M (2012) *Chin Chem Lett* 23:797
110. Albadi J, Keshavarz M, Shirini F, Vafaie-Nezhad M (2012) *Catal Commun* 27:17
111. Yamada YMA, Sarkar SM, Uozumi Y (2012) *J Am Chem Soc* 134:9285
112. Sharghi H, Khalifeh R, Doroodmand MM (2009) *Adv Synth Catal* 351:207
113. Kidwai M, Jain A (2011) *Appl Organomet Chem* 25:620
114. Meng X, Xu X, Gao T, Chen B (2010) *Eur J Org Chem* 5409
115. Aufort M, Herscovici J, Bouhours P, Moreau N, Girard C (2008) *Bioorg Med Chem Lett* 18:1195
116. Lin Z, Yu D, Sum YN, Zhang Y (2012) *ChemSusChem* 5:625
117. Zhang Y, Yu D, Lin Z (2013) *WO* 6143
118. Dururkar KA, Gonnade RG, Ramana CV (2009) *Tetrahedron* 65:3974
119. Kolarovič A, Schnürch M, Mihovilovic MD (2011) *J Org Chem* 76:2613
120. Bolla K, Kim T, Song JH, Ham J, Lee S (2011) *Tetrahedron* 67:5556
121. Kim T, Song JH, Jeong KH, Lee S, Ham J (2013) *Eur J Org Chem* 3992
122. Alonso F, Moglie Y, Yus M, Radivoy G (2010) *Adv Synth Catal* 352:3208
123. Alonso F, Moglie Y, Radivoy G, Yus M (2011) *Org Biomol Chem* 9:6385
124. Qian W, Winterheimer D, Amegadzie A, Allen J (2012) *Tetrahedron Lett* 53:271
125. Pericherla K, Jha A, Khungar B, Kumar A (2013) *Org Lett* 15:4304
126. Li K, Chen J, Li J, Chen Y, Qu J, Guo X, Chen C, Chen B (2013) *Eur J Org Chem* 6246
127. Vachhani DD, Kumar A, Modha SG, Sharma SK, Parmar VS, Van der Eycken EV (2013) *Eur J Org Chem* 1223
128. Kumar D, Buchi Reddy V (2010) *Synthesis* 1687
129. Kumaraswamy G, Ankamma K, Pitchaiah A (2007) *J Org Chem* 72:9822
130. Rajender Reddy K, Uma Maheswari C, Rajgopal K, Lakshmi Kantam M (2008) *Synth Commun* 38:2158
131. Sharghi H, Beyzavi MH, Safavi A, Doroodmand MM, Khalifeh R (2009) *Adv Synth Catal* 351:2391

132. Boningari T, Olmos A, Reddy BM, Sommer J, Pale P (2010) *Eur J Org Chem* 6338
133. Roper S, Franz MH, Wartchow R, Hoffmann HMR (2003) *Org Lett* 5:2773
134. Kumar D, Buchi Reddy V, Varma RS (2009) *Tetrahedron Lett* 50:2065
135. Huang Y, Gard GL, Shreeve JM (2010) *Tetrahedron Lett* 51:6951
136. Zhang J, Wu J, Shen L, Cao S (2011) *Adv Synth Catal* 353:580
137. Conrad WE, Rodriguez KX, Nguyen HH, Fettinger JC, Haddadin MJ, Kurth MJ (2012) *Org Lett* 14:3870
138. Sreedhar B, Reddy PS, Kumar NS (2006) *Tetrahedron Lett* 47:3055
139. Chandrasekhar S, Basu D, Rambabu C (2006) *Tetrahedron Lett* 47:3059
140. Basavaiah D, Reddy BS, Lingam H (2013) *Tetrahedron* 69:10060
141. Lee IYC, Yu OJ, Lim H-J, Lee HW (2008) *Bull Korean Chem Soc* 29:723
142. Alonso F, Moglie Y, Radivoy G, Yus M (2013) *J Org Chem* 78:5031
143. Quan Z-J, Xu Q, Zhang Z, Da Y-X, Wang X-C (2013) *Tetrahedron* 69:881
144. Surendra Reddy P, Sreedhar B (2009) *Synthesis* 4203
145. Kamijo S, Jin T, Huo Z, Yamamoto Y (2002) *Tetrahedron Lett* 43:9707
146. Kamijo S, Jin T, Huo Z, Yamamoto Y (2003) *J Am Chem Soc* 125:7786
147. Kamijo S, Jin T, Huo Z, Yamamoto Y (2004) *J Org Chem* 69:2386
148. Kamijo S, Jin T, Yamamoto Y (2004) *Tetrahedron Lett* 45:689
149. Barral K, Moorhouse AD, Moses JE (2007) *Org Lett* 9:1809
150. Moorhouse AD, Moses JE (2008) *Synlett* 2089
151. Zhang F, Moses JE (2009) *Org Lett* 11:1587
152. Beckmann HSG, Wittmann V (2007) *Org Lett* 9:1
153. Lee C-T, Huang S, Lipshutz BH (2009) *Adv Synth Catal* 351:3139
154. Smith NM, Greaves MJ, Jewell R, Perry MWD, Stocks MJ, Stonehouse JP (2009) *Synlett* 1391
155. Suarez JR, Trastoy B, Porez Ojeda E, Maryn-Barrios R, Chiara JL (2010) *Adv Synth Catal* 352:2515
156. Fletcher JT, Reilly JE (2011) *Tetrahedron Lett* 52:5512
157. Tao C-Z, Cui X, Li J, Liu A-X, Liu L, Guo Q-X (2007) *Tetrahedron Lett* 48:3525
158. Mohammed S, Padala AK, Dar BA, Singh B, Sreedhar B, Vishwakarma RA, Bharate SB (2012) *Tetrahedron* 68:8156
159. Kumar AS, Reddy MA, Knorn M, Reiser O, Sreedhar B (2013) *Eur J Org Chem* 4674
160. Zhang J, Jin G, Xiao S, Wu J, Cao S (2013) *Tetrahedron* 69:2352
161. Crowley JD, Bandeen Pauline H, Hanton LR (2010) *Polyhedron* 29:70
162. Vantikommu J, Pallapothula VR, Palle S, Surendra Reddy P, Ramanatham V, Khagga M (2010) *Eur J Med Chem* 45:5044
163. Jansa P, Špaček P, Votruba I, Břehová P, Dračinský M, Klepetářová B, Janeba Z (2011) *Collect Czech Chem Commun* 13:1121
164. Rivara M, Amori L, Zuliani V, Patel MK (2012) *Bioorg Med Chem Lett* 22:6401
165. Luvino D, Amalric C, Smietana M, Vasseur J-J (2007) *Synlett* 3037
166. Maisonneuve S, Xie J (2009) *Synlett* 2977
167. Dai C, Cheng Y, Cui J, Wang B (2010) *Molecules* 15:5768
168. Chambers CS, Patel N, Hemming K (2010) *Tetrahedron Lett* 51:4859
169. Shi F, Waldo JP, Chen Y, Larock RC (2008) *Org Lett* 10:2409
170. Ankati H, Biehl E (2009) *Tetrahedron Lett* 50:4677
171. Li J, Wang D, Zhang Y, Li J, Chen B (2009) *Org Lett* 11:3024
172. Friscourt F, Boons G-J (2010) *Org Lett* 12:4936
173. Hwang S, Bae H, Kim S, Kim S (2012) *Tetrahedron* 68:1460
174. Chowdhury C, Mandal SB, Achari B (2005) *Tetrahedron Lett* 46:8531
175. Aranz A, Iglesias M, Pintado-Sierra M, Sanchez F, Corma A (2012) *Adv Synth Catal* 354:1347
176. Brahma K, Achari B, Chowdhury C (2013) *Synthesis* 545
177. Ellison A, Boyer R, Hoogestraat P, Bell M (2013) *Tetrahedron Lett* 54:6005
178. Dhondge AP, Afraj SN, Nuzlia C, Chen C, Lee G-H (2013) *Eur J Org Chem* 4119

179. Yan Z-Y, Zhao Y-B, Fan M-J, Liu W-M, Liang Y-M (2005) *Tetrahedron* 61:9331
180. Hassan S, Tschersich R, Müller TJJ (2013) *Tetrahedron Lett* 54:4641
181. Torkian L, Dabiri M, Bararjanian M, Salehi P (2011) *Helv Chim Acta* 94:1416
182. Qian W, Amegadzie A, Winternheimer D, Allen J (2013) *Org Lett* 15:2986
183. MaGeE DI, Salehi P, Dabiri M, Bahrarnnejad M (2013) *Synth Commun* 43:486
184. Stefani HA, Vasconcelos SNS, Souza FB, Manarin F, Zukerman-Schpector J (2013) *Tetrahedron Lett* 54:5821
185. Alcaide B, Aragoncillo C, Callejo R, Ruiz MP, Almendros P, Torres MR (2012) *J Org Chem* 77:6917
186. Qian W, Wang H, Allen J (2013) *Angew Chem Int Ed* 52:10992
187. Mohiuddin G, Reddy PS, Ahmed K, Ratnam CV (1987) *J Chem Res Miniprint* 1839
188. Mohiuddin G, Reddy PSN, Ahmed K, Ratnam CV (1988) *Indian J Chem Sect B* 27:187
189. Thomas AW (2002) *Bioorg Med Chem Lett* 12:1881
190. Molteni G, Buttero PD (2009) *Heterocycles* 78:2837
191. Mohapatra DK, Maity PK, Shabab M, Khan MI (2009) *Bioorg Med Chem Lett* 19:5241
192. Granger BA, Kaneda K, Martin SF (2011) *Org Lett* 13:4542
193. Majumdar KC, Ganai S (2013) *Synthesis* 2619
194. Majumdar KC, Ganai S (2013) *Tetrahedron Lett* 54:6192
195. Sunderhaus JD, Dockendorff C, Martin SF (2007) *Org Lett* 9:4223
196. Donald JR, Martin SF (2011) *Org Lett* 13:852
197. Donald JR, Wood RR, Martin SF (2012) *ACS Comb Sci* 14:135
198. Guggenheim KG, Toru H, Kurth MJ (2012) *Org Lett* 14:3732
199. Akritopoulou-Zanze I, Gracias V, Djuric SW (2004) *Tetrahedron Lett* 45:8439
200. Saeedi M, Mahdavi M, Foroumadi A, Shafiee A (2013) *Tetrahedron* 69:3506
201. Gracias V, Darczak D, Gasielcki AF, Djuric SW (2005) *Tetrahedron Lett* 46:9053
202. Nguyen HH, Palazzo TA, Kurth MJ (2013) *Org Lett* 15:4492
203. Arigela RK, Mandadapu AK, Sharma SK, Kumar B, Kundu B (2012) *Org Lett* 14:1804
204. Pirali T, Tron GC, Zhu J (2006) *Org Lett* 8:4145
205. Olesen PH, Sørensen AR, Ursø B, Kurtzhals P, Bowler AN, Ehrbar U, Hansen BF (2003) *J Med Chem* 46:3333
206. Pokhodylo NT, Matychuk VS, Obushak MD (2010) *Synth Commun* 40:1932
207. Pokhodylo NT, Matychuk VS, Obushak MD (2009) *J Comb Chem* 11:481
208. Niu T-F, Gu L, Yi W-B, Cai C, Wang L (2012) *Eur J Org Chem* 6767
209. Niu T-F, Lv M-F, Wang L, Yi W-B, Cai C (2013) *Org Biomol Chem* 1040
210. Niu T-F, Gu L, Yi W-B, Cai C (2012) *ACS Comb Sci* 14:309
211. Daiichi Seiyaku Co, Ltd (1987) US 4652646
212. Barili PL, Biagi G, Livi O, Mucci L, Scartoni V (1987) *J Heterocycl Chem* 24:997
213. Biagi G, Franchi M, Giorgi I, Livi O, Scartoni V (1989) *J Heterocycl Chem* 26:39
214. Biagi G, Giorgi I, Livi O, Scartoni V, Lucacchini A (1992) *Farmaco* 47:1457
215. Biagi G, Giorgi I, Livi O, Scartoni V, Breschi C (1995) *Farmaco* 50:659
216. Biagi G, Giorgi I, Livi O, Scartoni V, Lucacchini A (1996) *Farmaco* 51:395
217. Kuleshov KV, Adamov AV, Rodin OG, Perevalov VP, El'man AR (2002) *Pharm Chem J* 36:445
218. Institute of experimental botany ASCR (2004) WO 18473
219. Kuleshov KV, Borovkov KY, Rodin OG, Perevalov VP (2006) *Chem Heterocycl Comp* 42:246
220. Abbracchio M, Eberini I, Parravicini C, Martini C, Trincavelli ML, Daniele S (2012) WO 59869
221. Tennant G (1966) *J Chem Soc C* 2290
222. Sutherland DR, Tennant G (1974) *J Chem Soc Perkin Trans 1* 534
223. Biagi G, Giorgi I, Livi O, Scartoni V, Velo S (1996) *Farmaco* 51:131
224. Chambers MS, Collins IJ, Goodacre SC, Hallett DJ, Jones P, Keown LE, Maxey RJ, Street LJ (2003) US 45532 Merck Sharp and Dohme Ltd (2002) US 6337331

225. Jones P, Chambers M (2002) *Tetrahedron* 58:9973
226. Pokhodylo NT, Matiychuk VS, Obushak NB (2009) *Chem Heterocycl Comp* 45:483
227. Pokhodylo NT, Matiychuk VS (2010) *J Het Chem* 47:415
228. Biagi G, Giorgi I, Livi O, Scartoni V, Velo S (1996) *Farmaco* 51:13
229. Bertelli L, Biagi G, Giorgi I, Livi O, Manera C, Scartoni V, Lucacchini A, Giannaccini G, Barili PL (2000) *Eur J Med Chem* 35:333
230. President and fellows of Harvard College (2009) WO 151561
231. Lee K, Campbell J, Swoboda JG, Walker S, Cuny GD (2010) *Bioorg Med Chem Lett* 20:1767
232. Ivachtchenko AV, Golovina ES, Kadieva MG, Koryakova AG, Mitkin OD, Okun IM, Tkachenko SE, Kovalenko SM, Ravnyeyko IM, Zaremba OV (2010) *J Comb Chem* 12:445
233. Porter TC, Smalley RK, Teguche M, Purwono B (1997) *Synthesis* 773
234. Shen HC, Ding F-X, Deng Q, Hammond ML, Tata JR, Colletti SL, Wilsie LC, Krsmanovic ML, Taggart AK, Ren N, Cai T-Q, Wu T-J, Wu KK, Waters MG, Carballo-Jane E, Cheng K, Chen Q, Wolff MS, Tong X, Holt TG (2009) *J Med Chem* 52:2587
235. Merck And Co, Inc (2006) WO 52555
236. Smith CJ, Nikbin N, Ley SV, Lange H, Baxendale IR (2011) *Org Biomol Chem* 9:1938
237. Smalley RK, Teguche M (1990) *Synthesis* 654
238. Westerlund C (1980) *J Heterocycl Chem* 17:1765
239. Pokhodylo NT, Matiychuk VS, Obushak ND (2009) *Chem Heterocycl Comp* 45:881
240. Lauria A, Patella C, Abbate I, Martorana A, Almerico AM (2013) *Eur J Med Chem* 65:381
241. Ivachtchenko AV, Golovina ES, Kadieva MG, Koryakova AG, Mitkin OD, Okun IM, Tkachenko SE, Kovalenko SM, Ravnyeyko IM, Zaremba OV (2010) *Bioorg Med Chem* 18:5282
242. Anderson MO, Zhang J, Liu Y, Yao C, Phuan P-W, Verkman AS (2012) *J Med Chem* 55:5942
243. Kim J, Kwon J, Lee D, Jo S, Park D-S, Choi J, Park E, Hwang JY, Ko Y, Choi I, Ju MK, Ahn JY, Kim J, Han S-J, Kim T-H, Cechetto J, Nam J, Ahn S, Sommer P, Liuzzi M, No Z, Lee J (2013) *Bioorg Med Chem Lett* 23:15
244. Pokhodylo NT, Matiychuk VS, Obushak MD (2009) *Tetrahedron* 65:2678
245. Pokhodylo NT, Shyyka OY, Savka RD, Obushak MD (2010) *Phosphorus Sulfur Silicon Relat Elem* 185:2092
246. Lauria A, Diana P, Barraja P, Almerico AM, Cirrincione G, Dattolo G (2000) *J Het Chem* 37:747
247. Lauria A, Diana P, Barraja P, Montalbano A, Cirrincione G, Dattolo G, Almerico AM (2002) *Tetrahedron* 58:9723
248. Lauria A, Patella C, Diana P, Barraja P, Montalbano A, Cirrincione G, Dattolo G, Almerico AM (2003) *Heterocycles* 60:2669
249. Lauria A, Patella C, Diana P, Barraja P, Montalbano A, Cirrincione G, Dattolo G, Almerico AM (2006) *Tetrahedron Lett* 47:2187
250. Lauria A, Patella C, Dattolo G, Almerico AM (2008) *J Med Chem* 51:2037
251. Khan MA, Fereitas ACC (1980) *J Het Chem* 17:1603
252. Lauria A, Abbate I, Patella C, Gambino N, Silvestri A, Barone G, Almerico AM (2008) *Tetrahedron Lett* 49:5125
253. Freitas AP, Proenca MFJRP, Booth BL (1995) *J Het Chem* 32:457
254. L'abbé G, Godts F, Toppet S (1985) *Bull Soc Chim Belg* 94:441
255. L'abbé G, Godts F, Toppet S (1985) *J Chem Soc, Chem Comm* 589
256. L'abbé G, Godts F, Toppet S, Meervelt LV, King GSD (1987) *Bull Soc Chim Belg* 96:587
257. Aoyama T, Kabeya M, Shioiri T (1985) *Heterocycles* 23:2371
258. Armstrong DR, Davies RP, Haigh R, Hendy MA, Raithby PR, Snaith R, Wheatley AEH (2003) *Eur J Inorg Chem* 3363
259. Boehringer Ingelheim Pharma GmbH And Co Kg (2005) WO 118575
260. De La Rosa M, Girardet J-L (2010) WO 135530

Top Heterocycl Chem (2015) 40: 325–378

DOI: 10.1007/7081_2014_121

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Published online: 15 March 2014

1,2,3-Triazoles Fused to Aromatic Rings

Belén Abarca and Rafael Ballesteros-Garrido

Abstract The structure, synthesis, reactivity and applications of 1,2,3-triazoles fused to aromatic rings are described. These compounds have been classified in two groups by a structural approach: (a) fused 1,2,3-triazoles without a bridgehead nitrogen atom and (b) fused 1,2,3-triazoles with a bridgehead nitrogen atom. Although both systems present a similar structure, the synthetic procedures and their reactivity are different.

Keywords 1,2,3-Triazoles · Benzotriazoles · Triazolopyridines · Triazolopyrimidines

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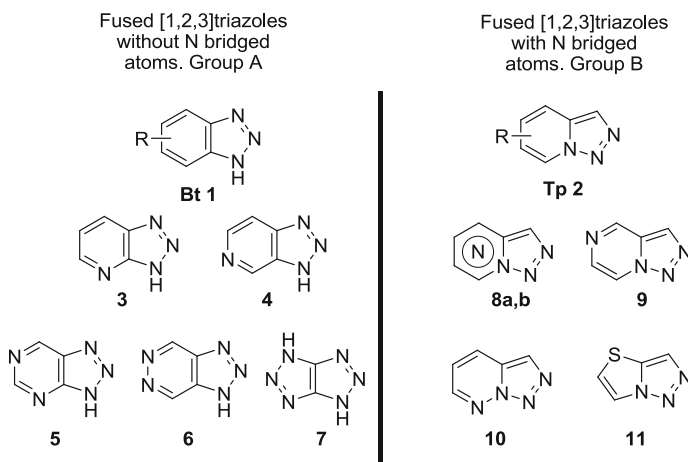
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Abbreviations

2-PyCHO	2-Pyridylcarboxyaldehyde
AIBN	Azobisisobutyronitrile
ArNs	Aromatic nucleophilic substitution
Boc	Tertbutoxycarbonyl
Bt	1 <i>H</i> -1,2,3-Benzotriazol
BuLi	Butyllithium
Cod	Cyclooctadiene
DMAD	Dimethyl acetylenedicarboxylate
DMF	Dimethylformamide
El	Electrophile
Et	Ethyl
FVT	Flash vacuum thermolysis
LDA	Lithium diisopropylamide
LiTMP	Lithium tetramethylpiperidine
NBS	<i>N</i> -Bromosuccinimide
NHC	<i>N</i> -heterocyclic carbene
NMR	Nuclear magnetic resonance
NOS	Nitric oxide synthase
Nu	Nucleophile
OAc	Acetoxy
Ph	Phenyl
THF	Tetrahydrofuran
TMSCN	Trimethylsilyl cyanide
TMSN ₃	Trimethylsilyl azide
Tp	[1,2,3]triazolo[1,5- <i>a</i>]pyridine
TPT	Triazolopyridine-pyridine-triazolopyridine
TsN ₃	Tosyl azide

1 Introduction

Fused 1,2,3-triazoles represent a large family of compounds that are applied in different scientific fields, covering from organic synthesis until copper conservation or highly energetic materials. The scope of the fused triazoles treated in this chapter involves systems with two aromatic rings of which one is a 1,2,3-triazole ring and the other is a six-membered aromatic ring. Such compounds have extensively been reviewed in the Comprehensive Heterocyclic Chemistry collection [1, 2]. In order to classify these compounds a structural approach has been reported: (a) Compounds without any bridged nitrogen atom, and the simplest structure is benzotriazole (**Bt**, **1**) reported by Chattaway and Orton in 1901 [3] (Fig. 1). This compound was initially named as azimido benzene. (b) Compounds with one of the three nitrogen acting as a bridge atom, with [1,2,3]triazolo[1,5-*a*]pyridine (**Tp**, **2**) as

**Fig. 1** 1,2,3-Triazoles fused to aromatic rings**Fig. 2** Fused 1,2,3-triazoles classification

the simplest compound of the group. The first report concerning this structure was the corresponding protonated compound reported in 1953 by Kuhn and Munzing [4]. Although both systems present a similar structure, the synthetic approaches towards them and their reactivity show themselves to be completely different.

2 1,2,3-Triazoles Fused to Aromatic Rings, Structure and Classification

Fused 1,2,3-triazoles having no nitrogen bridge atoms are a large family of compound with benzotriazole **1** as the most studied. The fusion of 5- and 6-membered aromatic rings, with the former 1,2,3-triazole, allows the possibility of another heterocyclic ring (i.e. pyridine) replacing benzene. [1,2,3]Triazolo[4,5-*b*] pyridine (**3**) or [1,2,3]triazolo[4,5-*c*]pyridine (**4**) are the closest systems to **1** reported in the literature (Fig. 2). [1,2,3]Triazolo[4,5-*d*]pyrimidine (**5**) and [1,2,3]-triazolo[4,5-*d*]pyridazine (**6**) systems are also included in this group (Fig. 2). Although these compounds represent the majority of the reported structures, some examples of fused 5+5 aromatic ring **7** can also be found in the literature; however, they are rare structures not deeply investigated compared to the 5+6 family.

The second family of fused 1,2,3-triazoles involves the sharing of one of the 1,2,3-triazole nitrogen atoms by both aromatic rings (either 6+5 or 5+5). As

mentioned before, the simplest compound of this group is [1,2,3]triazolo[1,5-*a*]pyridine (**2**, **Tp**). In this family, pyrimidine [1,5-*a*] (**8a**) and [1,5-*c*] (**8b**), pyrazine (**9**) and pyridazine (**10**) derivatives have also been reported and even some examples of 5+5 systems **11**. This family has been significantly less applied in comparison to the benzotriazole analogues, although they have interesting properties due to the presence of the nitrogen atom in both aromatic rings.

3 Group A: Fused 1,2,3-Triazoles Without a Bridgehead Nitrogen Atom

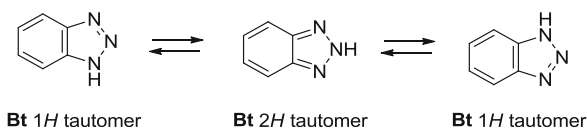
3.1 Structure: Tautomerism and Ring-Chain Isomerization

The particular arrangement of the three nitrogen atoms of benzotriazole gives rise to a special feature for these compounds. Firstly, benzotriazole shows proton tautomerism (Scheme 1). 1*H* and 2*H* **Bt** structures are in equilibrium. Wofford et al. reported in 1982 that in solution the 1*H* tautomer is the major compound [5]. However, several studies indicate that the 2*H* tautomer is observed in the gas phase at 0°K, with tautomer 1*H* increases its population at higher temperature. In terms of lone pair repulsion, it is clear that the 2*H* tautomer is more stable; however, theoretical calculations indicate that the more stable is the 1*H* tautomer [6].

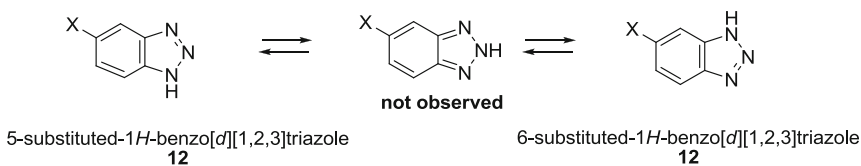
This particular characteristic has consequences for the benzotriazole nomenclature, and as long as two 1*H* structures are possible (Scheme 2), the mixture of them must be specified, for example, 5(6)-substituted-1*H*-benzotriazole (**12**).

This kind of phenomena is also present in *N*-alkylated benzotriazoles (Scheme 3). Known as cationtropic tautomerism and initially reported by Katritzky, this peculiarity allows the equilibrium between 1*N* and 2*N* alkylated **Bt**. *N*-Dialkylmethyl-aminobenzotriazole **13** exists as the N1 isomer in the solid state; however, in solution (in nonpolar solvents) or the gas phase, both isomers are present in a 2:1 ratio [7]. Analogues with oxygen **14a** [8] or sulphur **14b** have also the same feature [9]; however, with these heteroatoms, the interconversion is less fast and both 1*N* and 2*N* systems can be isolated.

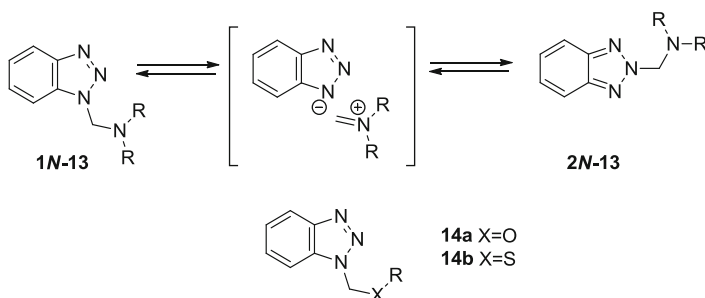
Benzotriazoles also present a particular property in their structures that has been less studied. Indeed they present an opened form in equilibrium with a closed form. Normally this equilibrium is completely on the closed form because of its larger stability. The open form may correspond to a molecule with resonance structures like an ortho-quinoid diazoimine and a benzene ring with a diazonium and an amide as substituents (Scheme 4). Although the detection of the opened forms remains difficult, Katritzky has reported one example with a compound that requires this form as the intermediate to explain the observed equilibrium between the two structures. The only possibility to go from structure **15A** to structure **15B** is through such opened form [10]. This isomerization, being anecdotic in the benzotriazole family, is very common in triazolopyridines (Scheme 4).



Scheme 1 Benzotriazole tautomerism



Scheme 2 Substituted benzotriazole tautomerism



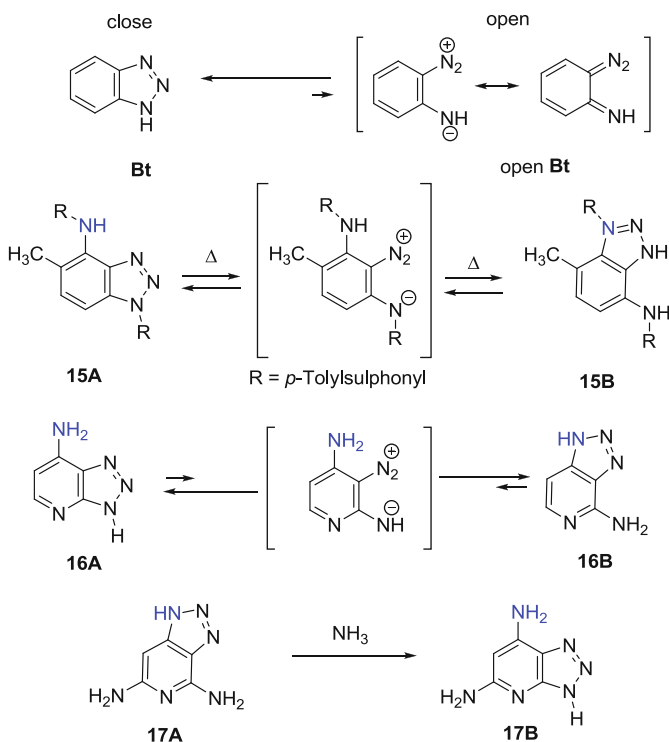
Scheme 3 Cationtropic tautomerism

For example, compound **16** is in equilibrium between **A** and **B** forms; hence it must be necessary to go through the open form [11]. Compound **17A** is also a good example of this ring-chain isomerization. In the presence of ammonia at 150°C, it converts into **17B** by means of an opened diazo system [12, 13].

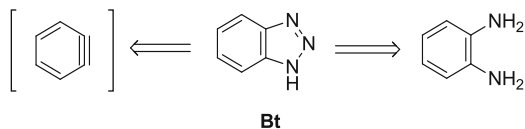
3.2 Synthesis of Benzotriazoles and Triazolopyridines

The preparation of benzotriazole can be realized by different strategies, either by [2+4] cycloaddition from an aryne or by the azotation of ortho-disubstituted diaminobenzene (Scheme 5). Interestingly, the most employed methodology relies on the use of ortho-diaminobenzenes as building blocks. Peterson reported in 1940 the protocol that has been employed for the preparation of benzotriazole and substituted benzotriazoles [14].

Some examples report the use of ortho-nitro anilines that are in situ reduced to obtain the diamine. Oxygenated derivative **18** was obtained during the formation of the triazole ring with hydrazine from 2-chloronitrobenzene [15].



Scheme 4 Ring-chain isomerization

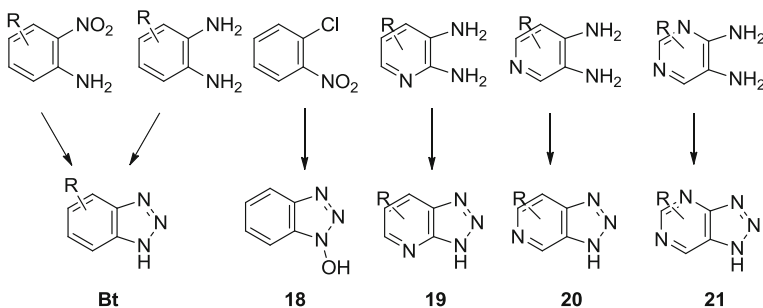
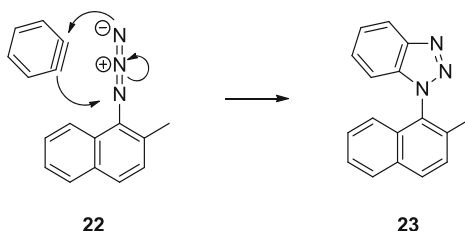
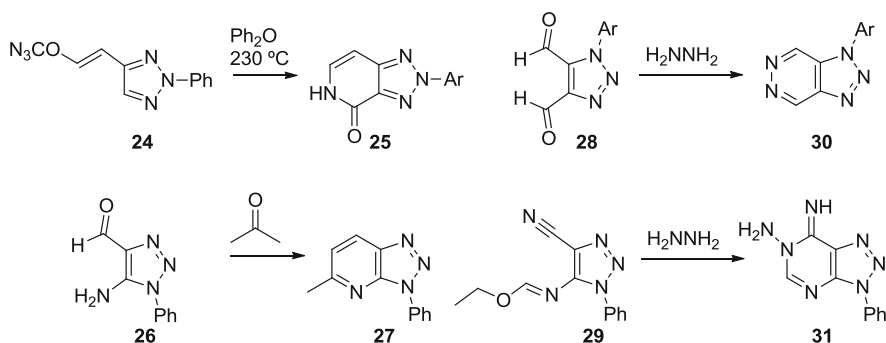


Scheme 5 Retrosynthetic approach

Applying a similar approach with the corresponding diamino derivatives, pyridine (**19**, **20**) and pyrimidine (**21**) derivatives were also obtained [16–19] (Scheme 6). This strategy can be applied to a large family of compounds and has allowed the preparation of more complex molecules derived from diamino pyridines [19, 20].

In the literature there are a few examples involving the aryne approach; however, they remain less employed. This 2+4 cycloaddition to obtain benzotriazoles was first reported by Kulagowski [21] (Scheme 7). Azide derivative **22** reacts with the corresponding aryne to form benzotriazole **23**.

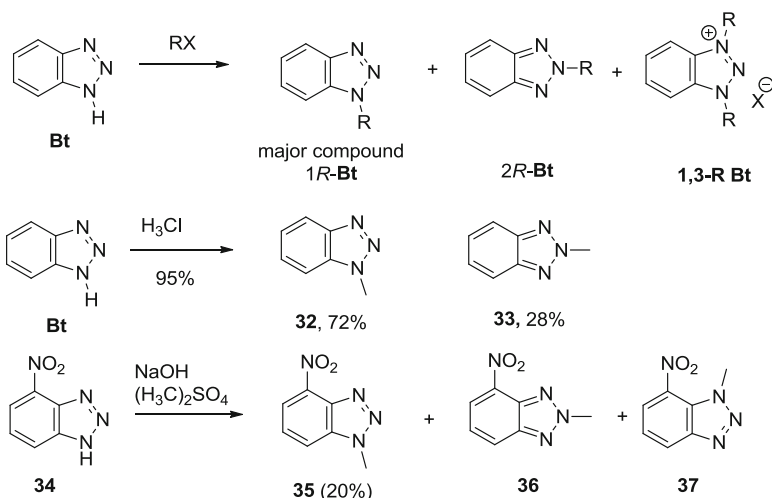
Despite these two strategies being the most common, some alternatives are possible with more complex heterocyclic compounds, based on the initial presence of the triazole ring in the reagent (Scheme 8). For example, triazole **24** undergoes cyclization to form compound **25** [22]. Treatment in acetone of compound **26** allows the formation of triazolopyridine **27** [23]. When 2 heteroatoms are present on the

**Scheme 6** Synthons for benzotriazoles and triazolopyridines**Scheme 7** Benzotriazole synthesis through arynes**Scheme 8** Alternative approach

6-membered ring, other strategies can be employed. In Scheme 8 we show that 1,2,3-triazoles **28** and **29** react with hydrazine to afford compounds **30** [24] and **31** [25].

3.3 Reactivity of Benzotriazoles and Triazolopyridines

The chemical reactivity of benzotriazoles and triazolopyridines can be presented in two parts: (1) functionalization of the triazole ring and the (2) functionalization of the benzene or heterocyclic (commonly pyridine) ring.

**Scheme 9** Alkylation of benzotriazoles

3.3.1 Functionalization of the Triazole Ring

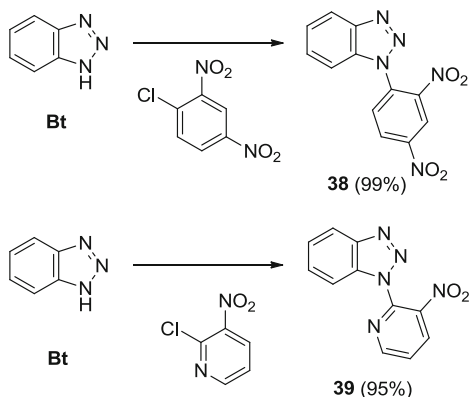
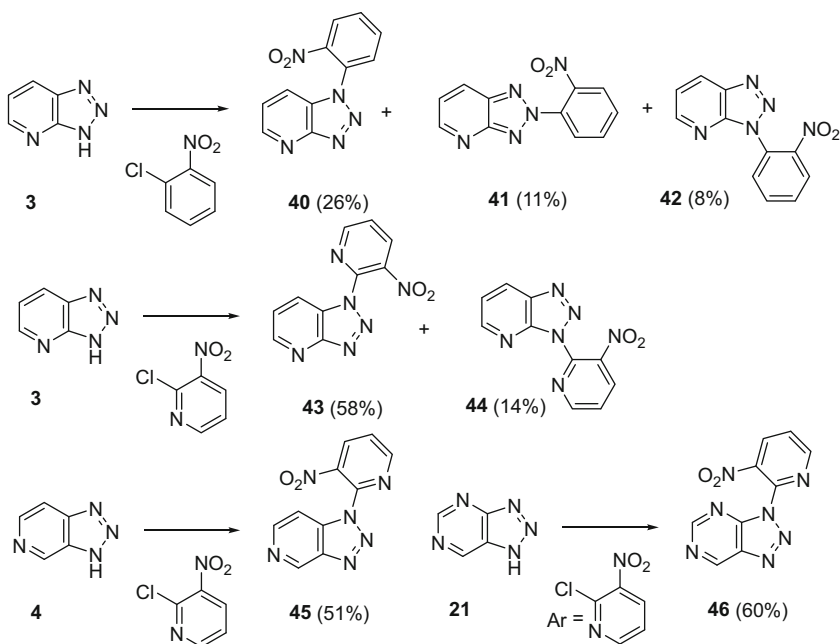
Alkylation

When **Bt** is reacted with alkyl halides, up to three compounds can be observed (Scheme 9): compounds derived from monosubstitution at position 1/3N (major) or 2N and, in some cases, 1,3-disubstituted compounds. Direct methylation of **Bt** affords with high yield (95%), a mixture between 1N-**32** and 2N-**33** methylated compounds in a 72/28 ratio [26]. However, the complexity of these reactions increases when benzotriazole has different substituents on the benzene ring (i.e. nitro substituent, compound **34**) (Scheme 9). In this compound N1 and N3 are no longer the same and the simplest reaction (i.e. methylation) affords at least 3 different compounds **35**, **36** and **37** [27].

Arylation

Bt acts as a nucleophile in aromatic nucleophilic substitution; exclusive substitution at 1N is observed. Reactions with chloronitrobenzenes are described, affording compounds **38** and **39** in high yields (Scheme 10) [28, 29].

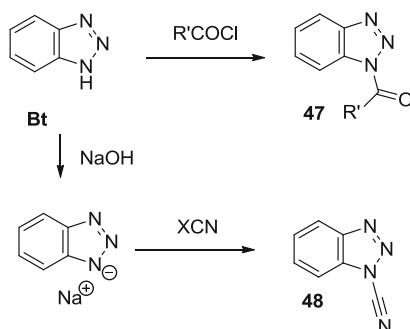
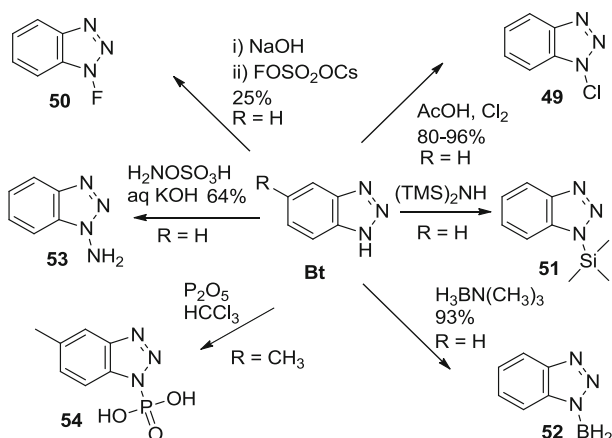
With triazolopyridine derivatives, this behaviour has also been observed. Although no direct reaction with methylene iodide has been reported, reactions with chloronitrobenzene or chloronitropyridine are present in the literature (Scheme 11). Triazolopyridine **3** reacts with either chloronitrobenzene or chloronitropyridine to form compounds **40**, **41** and **42** or **43** and **44** [30, 31]. In both cases the nitrogen atom from the triazole ring is more reactive than the one on the pyridine nitrogen. Triazolopyridine **4** reacts under similar conditions affording

**Scheme 10** Benzotriazole as nucleophile in ArNs**Scheme 11** Triazolopyridines and triazolopyrimidines as nucleophiles in ArNs

exclusively compound **45**. Triazolopyrimidine **21** affords **46** as a single compound in 60% [24].

N1 Functionalization by Different Substituents

Reaction of **Bt** with acyl chlorides allows the preparation of ketones/amides **47** [32]. Even the introduction of a cyano substituent has been achieved. When the

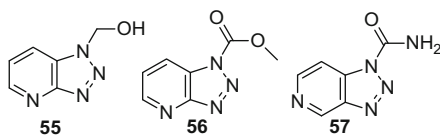
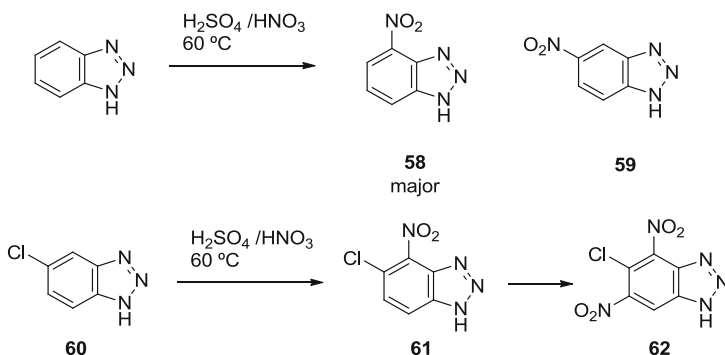
**Scheme 12** N1 functionalization**Scheme 13** N1 functionalization of **Bt** and methyl derivative

corresponding sodium salt of **Bt** is treated with $ClCN$ [33] or $BrCN$ [34], compound **48** is obtained (65 and 90%) (Scheme 12).

The introduction of other atoms has also been reported at position 1 (Scheme 13). Chlorination affords compound **49** in good yield [35]; fluorination [36] takes place with moderate yields affording **50** in 25%. Silylation and borylation have also been reported in the literature to form compounds **51** and **52** with moderate to good yields [37]. Amino and phosphorus derivatives **53** and **54** have also been reported in moderate to good yield [38, 39].

Some of these types of reactions have also been reported with triazolopyridines; shown in Fig. 3 are some of these less common compounds [38–42]. Compounds **55–57** are in agreement with the regioselectivity indicated before (Scheme 10).

At this point of the chapter, it is important to remark that almost all applications of **Bt** in organic synthesis deal with *N*-substituted **Bt**. Katritzky has reported many of these original contributions (more than 700) and has written several reviews covering the preparation and application of these compounds [32].

**Fig. 3** Triazolopyridine derivatives**Scheme 14** Nitration of Bt

3.3.2 Functionalization of the Benzene or Pyridine Ring

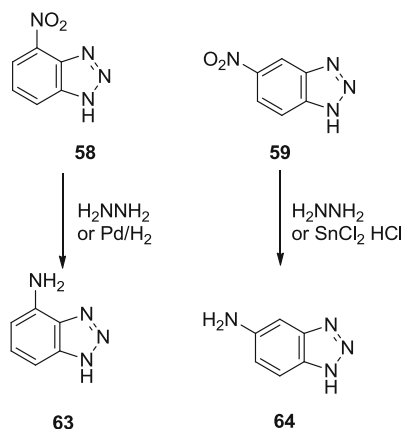
The introduction of functional groups on the benzotriazole trends to be performed on the benzene ring prior to the formation of the triazole ring. Nevertheless there are some reactions that are carried out on the benzotriazole ring that allow the functionalization of the benzene ring.

Nitration

Direct nitration of benzotriazole does indeed proceed at positions 4 and 5 with preference at the 4th position [10, 43]; thus compound **58** is the major isomer compared to **59** (Scheme 14). With chlorine-substituted systems **60**, mononitration [44] and dinitration [45] can be realized by increasing the temperature from 60 to 120°C , leading to compounds **61** and **62**. None of these reactions have been reported in the literature for triazolopyridines.

Amination

It remains essential to remark that no direct amination has been reported with benzotriazole. The reduction of nitro groups is the most employed strategy towards the synthesis of amino benzotriazoles (Scheme 15). Hydrazine or Pd/H_2 reductions are the most common methodologies to prepare 4-aminobenzotriazole **63** [10]. The

Scheme 15 Bt amino derivatives

derivative at position 5 compound **64** is less common and has been reported by reduction either with hydrazine or with SnCl_2 under acid medium [44, 46]. Those reduction conditions did not affect the benzene ring.

Halogenation

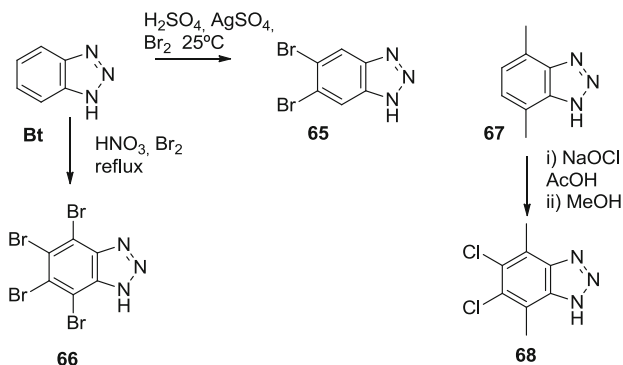
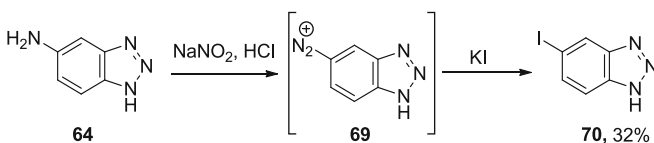
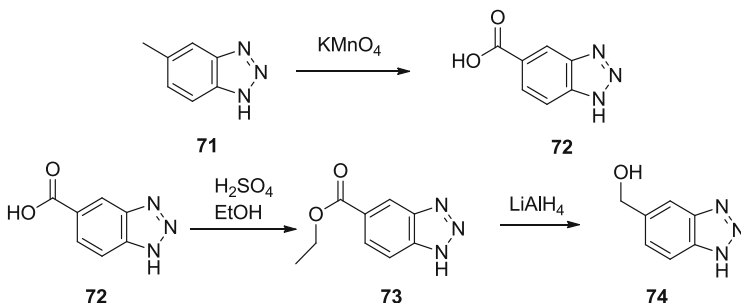
Direct halogenation has been mainly achieved with bromine leading either to dibromination at positions 5 and 6 (Scheme 16, compound **65**) or tetrabromination (compound **66**) with the harshest conditions [47]. The only example reported of chlorination is the reaction of 4,7-dimethyl benzotriazole **67** with NaOCl in acid medium [48]. Compound **68** is obtained under these conditions. No direct fluorination or iodination is reported.

An alternative approach towards the preparation of iodo derivatives relies on diazonium salts. Treatment of **64** with NaNO_2 affords the corresponding diazonium salt **69** that undergoes reaction with potassium iodide yielding the monoiodine derivative **70** in low yield (32%) (Scheme 17) [49].

Oxidation and Reduction

Oxidation and reduction are performed on the substituents attached to the benzotriazole ring. It has been reported that strong oxidation of 5-methyl benzotriazole **71** leads to the corresponding acid **72** in good yield (Scheme 18) [50]; however, extreme oxidant conditions can result in the complete destruction of the benzene ring as it will be shown later.

The structure of benzotriazole resists classical Fischer esterification conditions (H_2SO_4). Thus ester **73** has been reported [51]. Furthermore typical reduction reagents like LiAlH_4 allow reduction of functional groups without modification of the aromatic core, affording compound **74** [51] (Scheme 18).

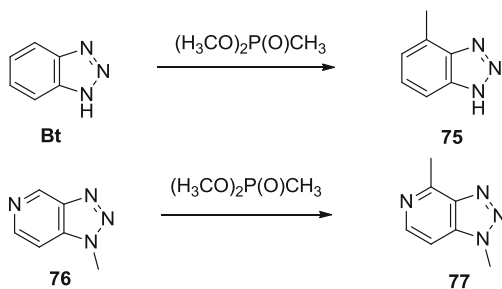
**Scheme 16** Halogenation of Bt**Scheme 17** Iodation of aminobenzotriazole**Scheme 18** Oxidation and reduction of benzotriazoles

Methylation

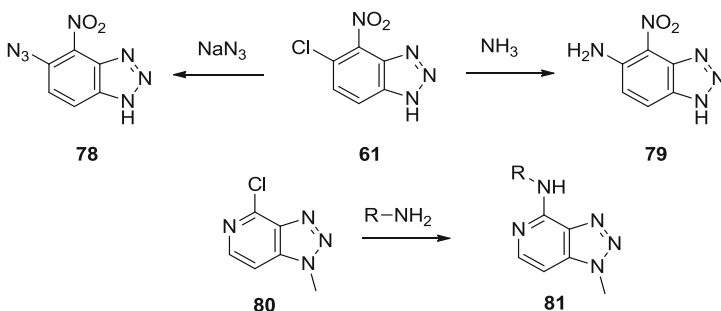
Methylation of benzotriazole has also been achieved in 80% yield by reaction with $(\text{H}_3\text{CO})_2\text{P}(\text{O})\text{CH}_3$ yielding to compound **75** (Scheme 19) [52]. These kinds of reactions are rarely reported in the literature with triazolopyridines; however, the regioselective methylation of compound **76** towards **77** [53, 54] has been described.

Aromatic Nucleophilic Substitution

Aromatic nucleophilic substitution has also been achieved with benzotriazoles but almost all examples required nitro groups to activate the system [45]. Compounds



Scheme 19 Methylations of **Bt** and methyl triazolopyridine **76**



Scheme 20 Aromatic Nucleophilic Substitution

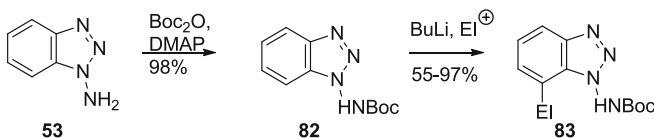
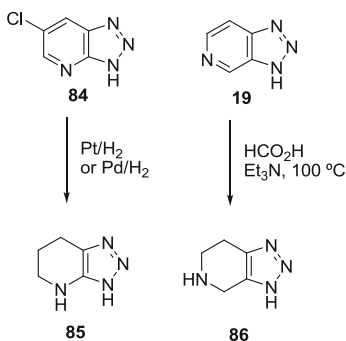
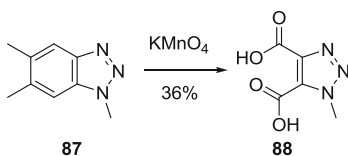
78 and **79** are obtained by means of this reaction (Scheme 20). Some examples are also reported with chlorinated triazolopyridines. Compound **80** undergoes aromatic nucleophilic substitution with primary amines leading to **81** [54].

Lithiation

Benzotriazole can also be functionalized by reaction with BuLi ; however, it requires Boc protection of 1N (Scheme 21). The only reported example is from compound **53**. After Boc protection (compound **82**), regioselective lithiation and subsequent trapping have been performed, affording compound **83** [38].

Hydrogenation

As apparent from the examples above, the benzene ring from **Bt** resists many different conditions. No references concerning the hydrogenation of this compound or derivatives have been reported. However, triazolopyridine derivatives undergo hydrogenation under particular conditions (Scheme 22). Compounds **84** and **19** under reducing conditions result in triazolopiperidines **85** and **86** [16, 56].

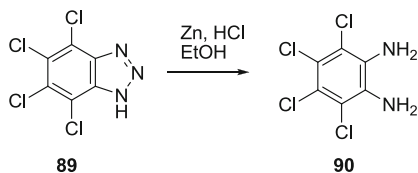
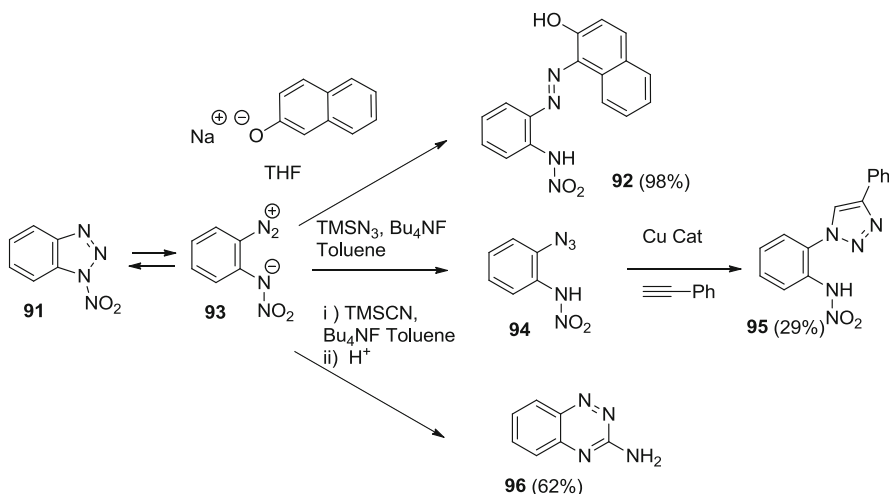
**Scheme 21** Lithiation of compound **53****Scheme 22** Hydrogenation of triazolopyridines**Scheme 23** Oxidation of benzene ring

3.3.3 Triazole Ring-Opening Reaction

The triazole ring in **Bt** is very stable as it can be seen by means of the reaction conditions reported in the previous examples. As an example, it is interesting to show that extreme oxidative conditions lead to the destruction of the benzene ring instead of the triazole one. Compound **87** affords triazole **88** under strongly oxidative conditions (Scheme 23) [57].

However, some reactions are reported that involve the destruction of the triazole ring leading to a benzene system. For example, tetrachlorobenzotriazole **89** reacts under strongly reducing conditions, affording the corresponding diamine **90** [58] (Scheme 24).

A second example of a ring-opening reaction starts from nitro compound **91** [59]. The presence of the nitro substituent destabilizes the triazole ring, and some ring-opening reactions have been reported [60]. Adduct **92** can be obtained in excellent yield via azo coupling reaction of intermediate diazonium salt **93** with the basic form of naph-2-ol. The formation of this compound can be explained

**Scheme 24** Opening of the triazole ring in **89****Scheme 25** Opening of the triazole ring in **91**

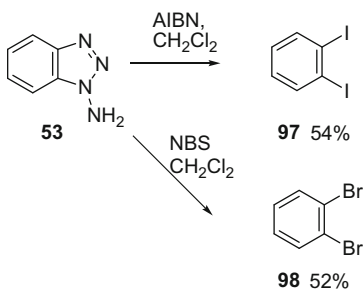
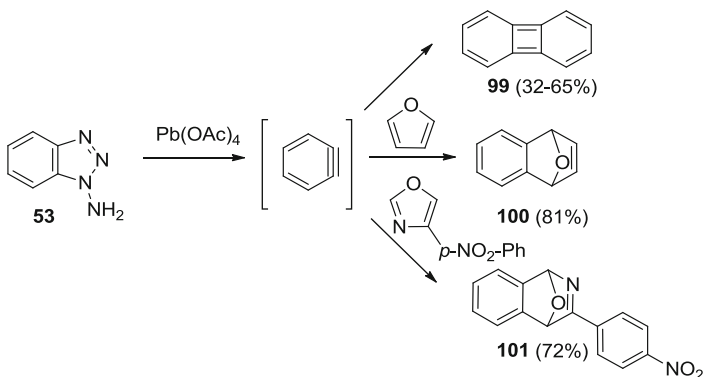
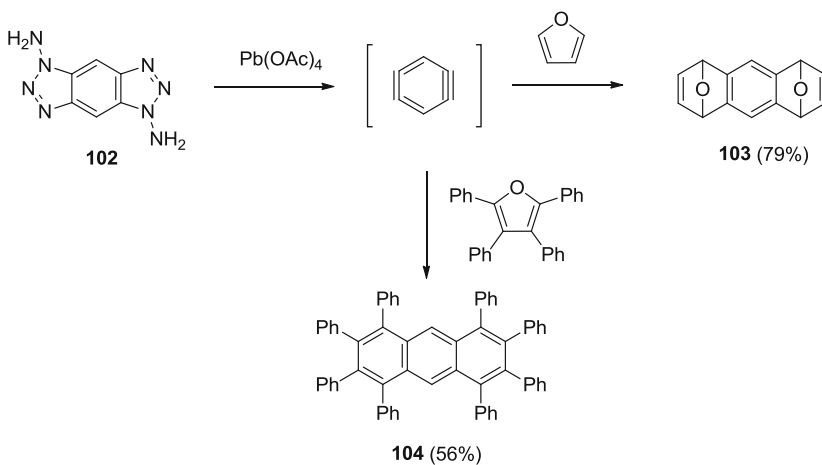
through an open form of **91** with the structure **93**. This ionic form can undergo direct ArNs, leading to compound **94** that was subsequently transformed into a triazole by means of click chemistry (compound **95**). Finally, compound **91** has also been reported as a precursor of exotic heterocyclic compounds like **96** (Scheme 25).

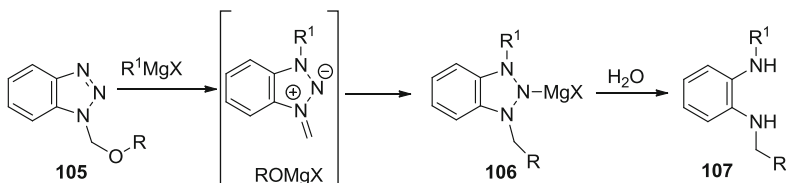
1-Aminobenzotriazole **53** has a particular and interesting behaviour [61, 62] (Scheme 26) giving diiodobenzene **97** and dibromobenzene **98** in moderate yields by radical reactions.

This amino derivative allows the generation of an aryne as the intermediate in the presence of lead acetate (Scheme 27). Despite not being the most employed aryne source, some examples have been reported [63–65]. Adduct **99** that combines two arynes can be obtained in moderate yield. In a similar way, reaction with furan or oxazole leads to the corresponding cycloaddition adducts **100** and **101** in good yields.

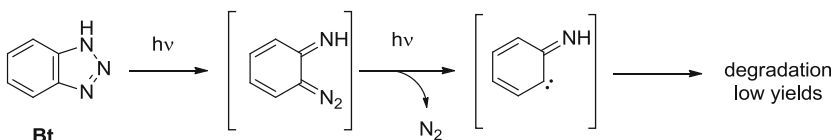
Even more surprisingly, diaminobistriazole **102** also shows this behaviour [66] (Scheme 28). This compound performs double-aryne generation, affording more complex structures in moderate to good yields. Adducts **103** and **104** are obtained with good yields.

Another approach towards the cleavage of the triazole ring relies on the preparation of salts. Grignard addition to compound **105** generates intermediate **106** that

**Scheme 26** Triazole ring opening in 1-aminobenzotriazole **53****Scheme 27** Aminobenzotriazole **53** as aryne source**Scheme 28** Diaminobistriazol **102** as double-aryne source



Scheme 29 Benzodiamine **107** preparation from benzotriazole **105**



Scheme 30 Photochemical decomposition of **Bt**

in the presence of water decomposes towards the diamine derivative **107** (Scheme 29) [67]. However, the presence of the ether moiety is required for this reactivity.

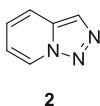
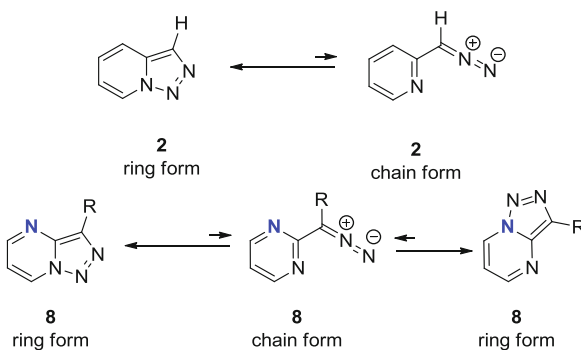
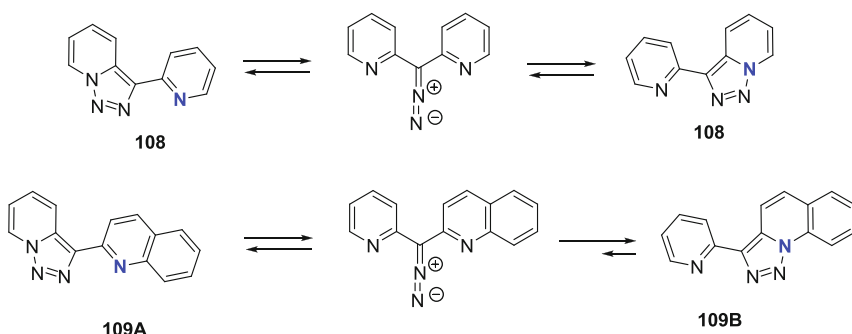
An alternative towards the activation of the triazole ring is the photochemical approach; nevertheless, benzotriazole shows itself to be extremely stable, and low yields are obtained of the corresponding photodegradation products from nitrogen elimination [68] (Scheme 30).

4 Group B: Fused 1,2,3-Triazoles with a Bridgehead Nitrogen Atom

Fused 1,2,3-triazoles with a bridgehead nitrogen atom are those systems when one of the three nitrogen atoms from the triazole ring belongs also to the second aromatic ring. As it has been outlined before, these compounds are represented by the parent [1,2,3]triazolo[1,5-*a*]pyridine (Fig. 4). This compound **Tp** is the simplest member of this family, and although having similar features like benzotriazole, it has also particular characteristics that are not present in the **Bt** family.

4.1 Structure: Tautomerism and Ring-Chain Isomerization

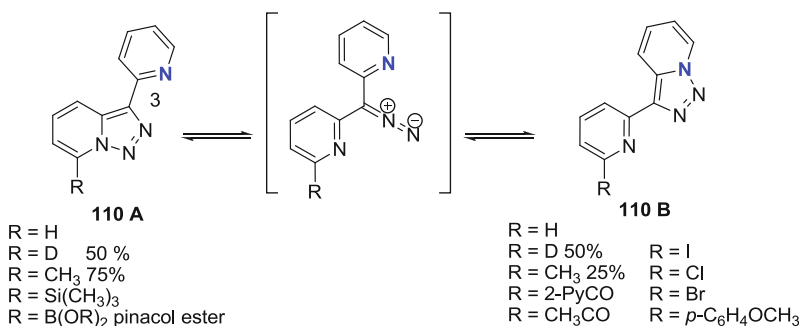
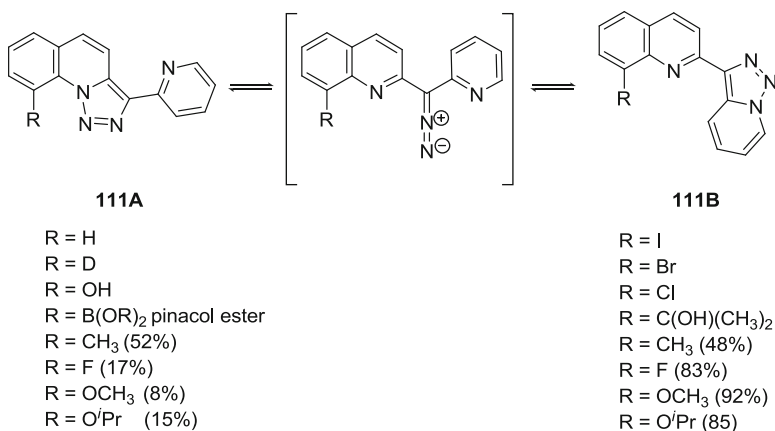
Compared to the benzotriazole family, these compounds do not present H-tautomerism. However, they indeed show also a ring-chain isomerization. This phenomenon is even more common than in the **Bt** family (Scheme 31) [69]. The

**Fig. 4** Parent compound of the [1,2,3]triazolo[1,5-*a*]pyridine family**Scheme 31** Ring-chain isomerization in triazolopyridine **2** and triazolopyrimidine **8****Scheme 32** Ring-chain isomerization in triazolopyridines **108** and **109**

open chain form of these systems is a classic diazo compound. Triazolopyrimidine **8** also presents this equilibrium [70]. As it will be described later, these compounds can react like a diazo compound.

This phenomenon became even more interesting when the substituent R is a 2-pyridyl [71] **108** or 2-quinolyl [72] **109**, because then there are 2 structures in equilibrium. Through an open intermediate with a diazo structure, the cyclization can take place, involving one of the two different nitrogen atoms. Similarly to what has been reported with **Bt**, the most electron-rich nitrogen (or the less hindered) is preferred for the triazole ring formation (Scheme 32).

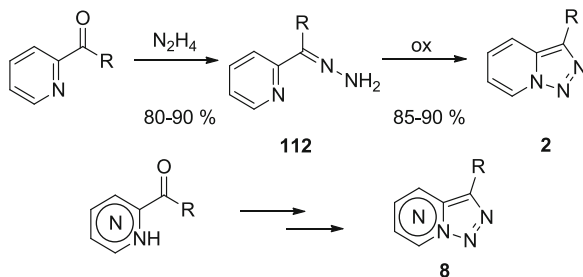
For 3-(2-pyridyl)-triazolopyridine **108**, both structures are exactly the same; however, in the case of potential equilibrium **109A** and **109B**, there is an interesting difference in the structure of both isomers. There are some studies about the

**Scheme 33** Ring-chain isomerization in 7-substituted -3-(2'-pyridil)-triazolopyridines **110****Scheme 34** Ring-chain isomerization in 9-substituted -3-(2'-pyridil)-triazoloquinolines **111**

ring-chain isomerism of 7-substituted-3-(2-pyridyl)-triazolopyridines **110** and 9-substituted-3-(2-pyridyl)-triazoloquinolines **111** [71, 72].

Traditionally these structures had been noted as **A** compounds for those bearing the substitution on the triazolopyridine (or triazoloquinoline) ring and **B** for those obtained after the isomerization. In compound **110** with a methyl group as substituent, a mixture of **A/B** products is observed, and although they can easily be identified by NMR (Scheme 33), these systems cannot be separated because they isomerize at room temperature. Theoretical calculations support these findings. Electronic properties of the substituent were found determinant. Electron-withdrawing substituents favour a **B** structure. Electron donors tend to result in the **A** structure.

Triazoloquinolinepyridines **111** behave similarly. However, initially both **A** and **B** structures are nonequivalent and only **A** is observed (Scheme 34). The introduction of a substituent modifies the **A/B** ratio. Also in this case, electron-withdrawing and bulky substituents afford the **B** structure, and small and donor substituents afford the **A** structure.

Scheme 35 General approach towards the synthesis of **2** and **8**

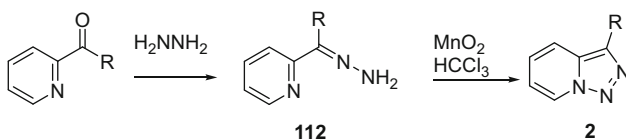
4.2 Synthesis

All examples concerning the synthesis of these compounds involve the preparation of α -substituted pyridines. Indeed pyridines are the major starting reagents for the preparation of **Tp**. There are several methodologies reported. The most common approach involves 2-pyridyl aldehydes or ketones that react with hydrazine leading to hydrazone **112** that then is submitted to oxidation (analogous to the Staudinger approach to diazo compounds) affording the desired compounds **2** (Scheme 35). This strategy is also employed for the other members of the families like triazolo[1,5-*a*] or [1,5-*c*]pyrimidines **8** [70, 73].

Boyer et al. [74] published the first synthesis of [1,2,3]triazolo[1,5-*a*]pyridines of type **2**. Hydrazones **112** were oxidized using Ag_2O to give the diazo intermediates which undergo an intramolecular cyclization, affording [1,2,3]triazolo[1,5-*a*]pyridines **2**. Although Ag_2O provided triazolopyridines in good yields, Boyer and Ramage [75] replaced it by potassium ferrocyanide. However, along with **2** several side reaction products were obtained. Many other oxidants, like nickel peroxide, lead tetraacetate and copper (I) salts, have been tested [76, 77]. Comparing all published synthetic ways to obtain [1,2,3]triazolo[1,5-*a*]pyridines using this methodology, the oxidation with manganese (IV) oxide (MnO_2) due to its low cost and the good and reproducible yields made it the reagent of choice. Manganese oxide was successfully employed by Abarca [78] to prepare triazolopyridines on gram scale (Scheme 36).

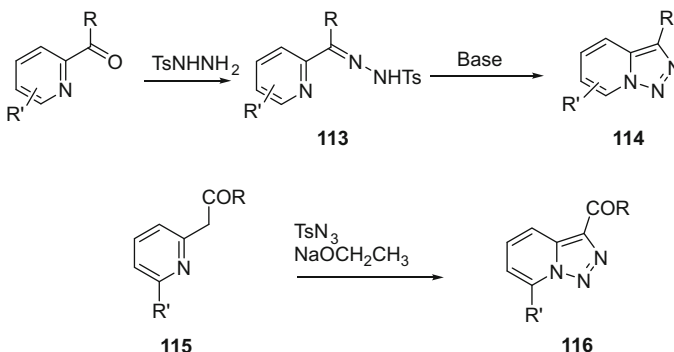
In order to avoid the oxidation step that can show incompatibilities with other functional groups, Boyer and Goebel [79] developed another variant of Bamford-Stevens approach to obtain triazolopyridines. They were synthesized after condensation of tosylhydrazine with the corresponding 2-pyridyl aldehydes or ketones. This reaction led to tosylhydrazones **113**. Following a basic treatment with NaOH or KOH, derivatives **114** were obtained. In this way, they succeeded in the synthesis of 3-phenyl, 3-picolinoyl and [1,2,3]triazolo[1,5-*a*]pyridines in high yields without use of oxidizing agent (Scheme 37). Other bases like morpholine were also employed to prepare, for example, 7-methyltriazolopyridine [80], 5-methoxytriazolopyridine [81] or their bromine analogues [82].

A third original approach relies on the reaction with azides. From 2-acylmethylpyridines **115** with tosylazide (TsN_3) in the presence of sodium

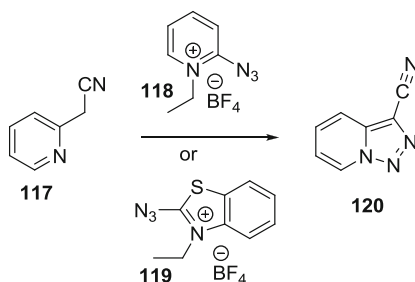


R = H, Me, Ph, 2-Pyridyl or 2-Thiophenyl

Scheme 36 Abarca approach to **Tp**



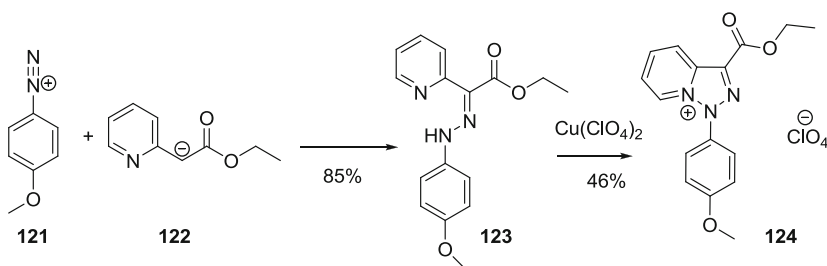
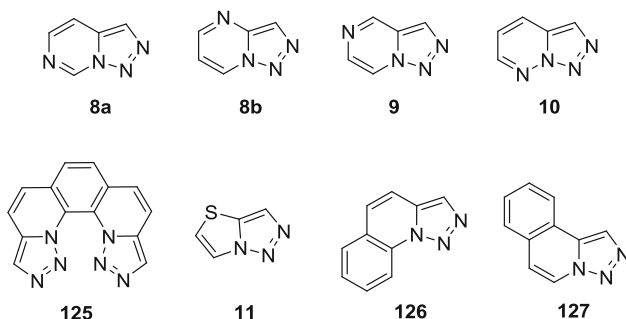
Scheme 37 Tosylhydrazine and Tosylazide approaches



Scheme 38 Preparation of **120**

ethoxide, Regitz obtained triazolopyridine derivatives with moderate to high yields (50–80%) [83, 84], compounds **116** were obtained by this procedure. From compound **117** and other different azides, like 2-azido-1-ethylpyridinium tetrafluoroborate **118** [85] or 2-azido-3-ethylbenzothiazolium tetrafluoroborate **119**, the cyano derivative **120** was obtained (Scheme 38) [86].

The previous strategies are the most commonly employed; however, some alternatives have also appeared that allow the formation of the 1,2,3-triazole ring with substitution at N1 [87]. This approach employs a diazo compound **121** that reacts with the anion **122** leading to a substituted hydrazine **123**. Oxidation with copper (II) perchlorate leads to the 1-substituted triazolopyridinium perchlorate salt **124** in moderate yield (Scheme 39).

**Scheme 39** Preparation of 1-substituted triazolopyridinium **124****Fig. 5** Different structures of **B** family

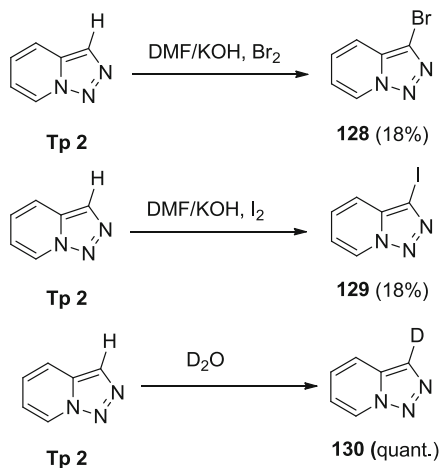
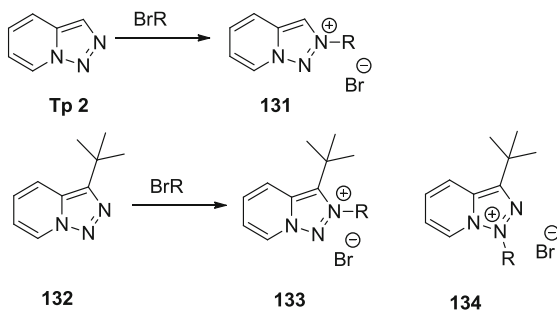
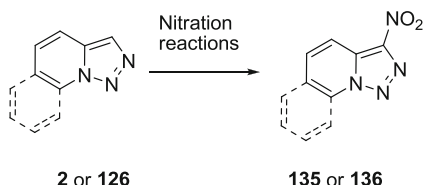
These strategies have been applied with different starting reagents. Although the number of examples synthesized is significantly smaller than in **Bt** family, some interesting structures **8–11** and **125–127** have been reported [70, 73, 74, 88–90] (Fig. 5).

4.3 Reactivity of the Triazolopyridines Family

4.3.1 Functionalization of the Triazole Ring

Halogenation

This family has significant differences in terms of reactivity regarding **Bt**. Triazolopyridine with no substituent at position 3 can be bromated or iodinated in basic medium, giving compounds **128** and **129** with moderate yields [91, 92]. It is also important to remark that the proton in position 3 is acidic and exchanges with deuterium just by heating in D_2O , leading to compound **130** (Scheme 40).

Scheme 40 Substitution at position 3 of parent compound **2****Scheme 41** Alkylation of **TP****Scheme 42** Nitration of **2** and **126**

Alkylation

Alkylation to give triazolopyridinium salts has also been reported on these systems. Normally they are alkylated at nitrogen 2, obtaining structures like compound **131**. However, with large substituents at position 3 [93, 94], like tert-butyl derivative **132**, mixtures of **133** (N2) and **134** (N1) alkylated products are observed (Scheme 41).

Nitration

Nitration of these systems with no substitution at position 3 can also be performed, affording nitrotriazolopyridines **135** [95] and nitrotriazoloquinolines **136**

[96]. However, these reactions gave low yields and side products derived from the opening of the triazole ring (Scheme 42) (see 4.3.3).

4.3.2 Functionalization of the Pyridine Ring

Lithiation

This family of compounds presents a general reactivity that is completely different from benzotriazoles. Indeed all triazolopyridines undergo regioselective metallation at position 7 with butyllithium [80]. Trapping with electrophiles allows the preparation of 7-substituted derivatives **137**. This regioselectivity can be explained by the directed effect by N1 towards peri-metallation (Scheme 43).

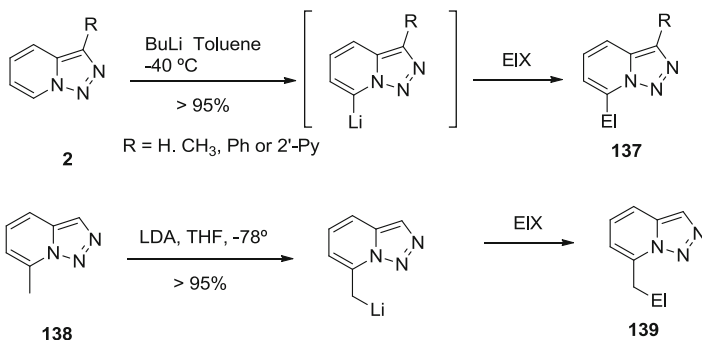
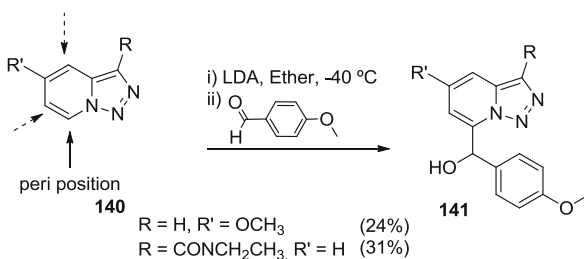
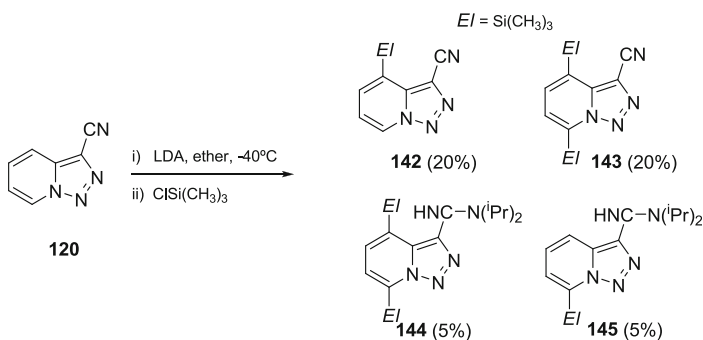
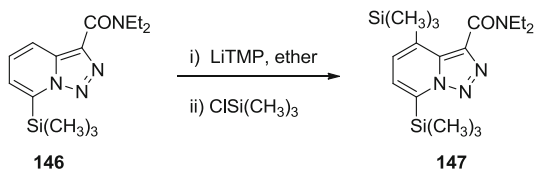
The regioselective metallation at position 7 has been employed for the preparation of a large variety of compounds. This includes also all compounds that were studied in the ring-chain isomerization (see Sect. 4.1 Schemes 33 and 34). This position is extremely activated, undergoing lithiation even when a methyl group is at this place, for example, in compound **138** leading to **139** [80, 97]. This result indicates how different can be the reactivity of **Bt** and **Tp** families. Some studies have been performed [81] by introducing *ortho*-directing groups to metallation on the triazolopyridine ring, like compound **140**, trying to get lithiation in different positions. Nevertheless the metallation with LDA provided exclusively 7-substituted triazolopyridines **141** (Scheme 44).

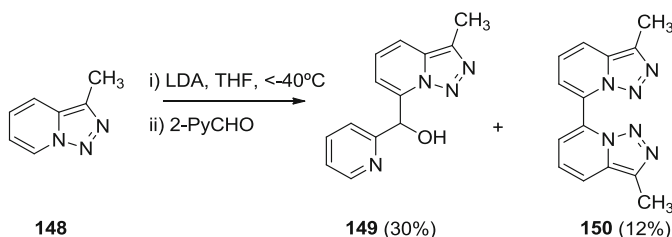
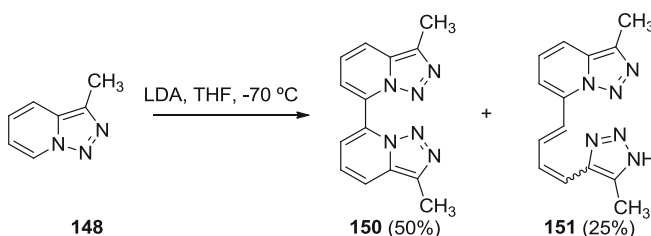
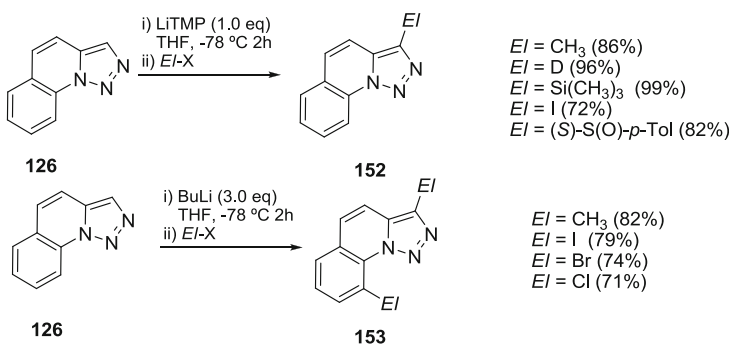
So far, only few examples of metallation at other positions were described in the literature. Nevertheless, in 1995, Jones reported the reaction of 3-cyano-[1,2,3]triazolo[1,5-*a*]pyridine **120** with LDA [98]. Although this reaction provides a complex mixture of products after trapping with trimethylsilyl chloride, 4-substituted triazolopyridine **142** was identified. However, the low yield remained an important drawback from a synthetic point of view (compound from dimetallation **143** was also isolated and some other side products like **144** and **145**) (Scheme 45).

As reported also by Jones, 4-substitution could be achieved with 7-trimethylsilyl-3-carboxamide-[1,2,3]triazolo[1,5-*a*]pyridine (**146**) but lead to compound **147** in very low yield (5%) [98] (Scheme 46).

One important reaction reported with lithium derivatives is the dimerization. Under specific conditions, heterocyclic π -deficient compounds can undergo dimerization. This kind of aryl-aryl coupling is known, but it was not intensively investigated. The reaction of dimerization of [1,2,3]triazolo[1,5-*a*]pyridines was observed by Abarca and Ballesteros for the first time in 1997 (Scheme 47). When 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine (**148**) was treated with LDA at -40°C in THF followed by trapping with 2-pyridylcarboxaldehyde, expected compound **149** was obtained. However, the corresponding dimer **150** was also obtained as a side product [99].

Due to the interesting structure of this dimer, the authors modified the reaction conditions in order to favour dimerization [82]. They found out that the optimal

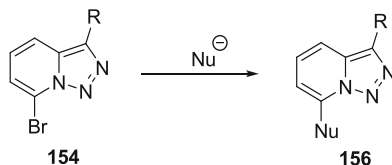
**Scheme 43** Regioselective metallation of **Tp****Scheme 44** Regioselective metallation of substituted **Tp****Scheme 45** Metallation of **120****Scheme 46** Metallation of **146**

**Scheme 47** First synthesis of **150****Scheme 48** Optimized synthesis of **150****Scheme 49** Mono- and dimetallation of **126**

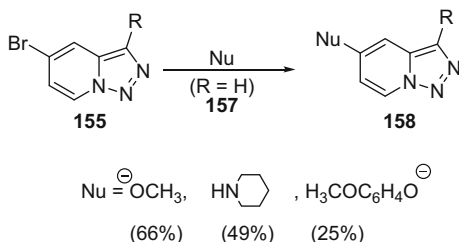
conditions were LDA (1 eq)/THF/ -70°C . After 9 h, the dimer **150** was obtained in a 50% yield, but surprisingly, another side product (1-(3-methyl-1,2,3-triazolo[1,5-*a*]pyridin-7-yl)-4-(5-methyl-1*H*-1,2,3-triazol-4-yl)-1,3-butadienyl) (**151**) was formed in a non-negligible amount (25%) (Scheme 48).

Other compounds of this group of fused 1,2,3-triazoles with a N-bridgehead tend to have particular reactivity. Indeed triazoloquinolines **126** can be metallated at position 3 with LiTMP giving compounds **152**, after trapping with electrophiles, in good yield. However, when 3 equiv. of BuLi are employed, double lithiation can be achieved, affording, after trapping, 3,9-disubstituted triazoloquinolines **153** [100] (Scheme 49).

Scheme 50 Aromatic nucleophilic substitution in C7



Scheme 51 Aromatic nucleophilic substitution in C5



Reactions with Nucleophiles

The [1,2,3]triazolo[1,5-*a*]pyridines do not react directly with nucleophiles. However, some ArNs reactions with the halogenated derivatives 7-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**154**) and 5-bromo-3-substituted-[1,2,3]triazolo[1,5-*a*]pyridines (**155**) are described [82, 101]. Compounds **154** react with nucleophiles like sodium methoxide, sodium 4-methoxyphenolate or sodium benzenethiolate in DMF at 90°C to give substituted compounds **156** in high yields. Also, in ethanol at 80°C, sodium hydrazine and sodium piperidine afforded substitution products **156** in respectively 60 and 65% yield. No reaction occurs with sodium azide and potassium cyanate [101] (Scheme 50).

5-Bromotriazolopyridine **157** reacts with nucleophiles allowing the functionalization at the C5 position leading to compounds like **158** [82] (Scheme 51). No reaction occurs when the reaction is carried out with the chlorinated derivative or with 6-bromo-[1,2,3]triazolo[1,5-*a*]pyridine.

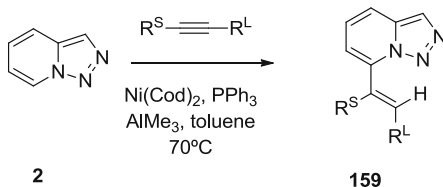
Position 7 of **Tp 2** has also been reported as suitable for direct CH activation in the presence of Ni(COD)₂ and disubstituted alkynes leading to compounds **159** in good yields (85–90%) [102] (Scheme 52).

Hydrogenation Reactions of Triazolopyridines

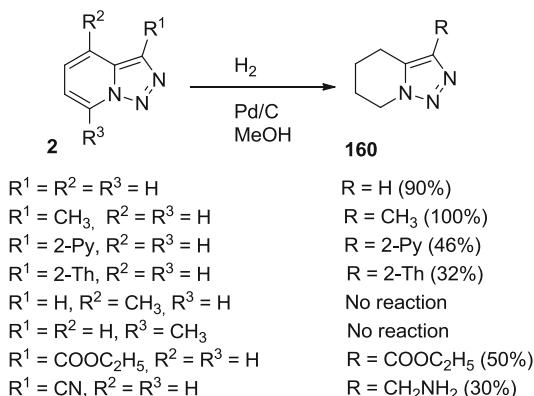
In 1999, Abarca et al. published a study on the hydrogenation of several triazolopyridines **2** by means of heterogeneous catalysis under mild conditions (Pd/C, methanol, 25°C, atmospheric pressure) and obtained 4,5,6,7-tetrahydrotriazolopyridines **160** as indicated in Scheme 53 [103]. This particular feature is completely different from benzotriazoles where the hydrogenation remains difficult and only was reported with some pyridine derivatives.

When the triazolopyridine is substituted by a methyl group in position 3, the reactions lead to the formation of the tetrahydro derivative in good yield. However,

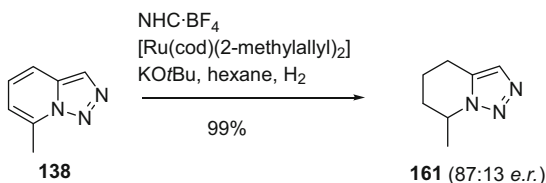
Scheme 52 Direct 7-CH activation (R^S small substituent, R^L large substituent)



Scheme 53 Heterogeneous hydrogenation



Scheme 54 Homogeneous hydrogenation

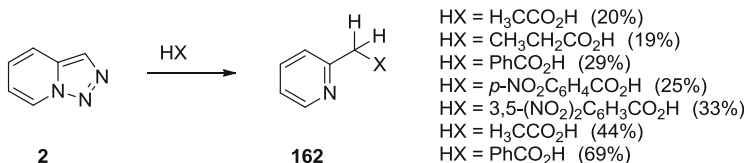


if the methyl group is on the pyridine ring, no hydrogenation product was observed and the starting material was recovered. When the pyridine is substituted with a thiophene at position 3, the 4,5,6,7-hydrogenated product was obtained in low yield (32%) even with increased catalyst charge. This can be explained by the poisoning effect of sulphur towards palladium. On the other hand, the authors highlighted that the presence of electron-withdrawing substituents at the C3 position decreases the reactivity towards hydrogenation.

Recently Glorius has reported a homogeneous hydrogenation of substituted triazolopyridines **138** in excellent yields and high enantiomeric ratio (*e.r.*) by means of Ru NHC complexes to obtain triazolopiperidines **161** (Scheme 54) [97].

4.3.3 Opening Reactions of the Triazole Ring in Triazolopyridines

Triazolopyridine **2** and its derivatives undergo triazole ring-opening reaction with loss of dinitrogen in many different conditions. These compounds tend to afford pyridines in the presence of acids. The first paper about this was published by Boyer



Scheme 55 Triazole ring-opening reaction with organic acids

and Wolford in 1958. In their study [104], with carboxylic acids at high temperature, the triazole ring degrades with loss of dinitrogen to provide pyridine esters **162** in moderate yields (Scheme 55).

Jones performed an exhaustive and methodological study [105] about the ring-opening reaction with loss of nitrogen molecule with electrophiles like sulphuric acid, acetic acid, halogens (Cl_2 and Br_2) and selenium dioxide (Table 1).

Reaction with bromine and iodine has also described with compound **163**, giving the formation of the corresponding derivatives **164** and **165** [106] (Scheme 56).

Abarca and Ballesteros also studied the ring-opening reaction of triazolopyridine dienic derivatives **166** and **167** in sulphuric acid, acetic acid and selenium (IV) oxide [99] (Scheme 57). These reactions afford the corresponding alcohols **168** and **169** with sulphuric acid; esters **170** and **171** were obtained with acetic acid. With selenium oxide, however, compound **166** does not react, but **167** gives the corresponding ketone **172**.

As it has been noted before, the triazolopyridines can be in equilibrium with an opened form. This form is a diazo compound; thus reactivity similar to diazo compounds should be observed. This behaviour was initially reported by Wentrup in the 1960s–1970s [91]. Flash vacuum thermolysis of compound **173** affords complex compound **174** that is explained by means of the chemistry of diazo form **175** (Wolff rearrangement) [107] (Scheme 58).

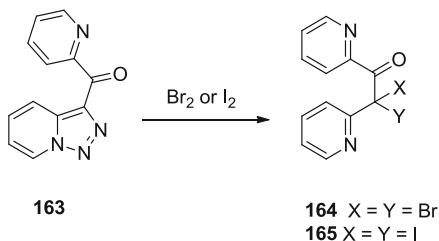
Other reaction reported in the literature by Wentrup is the thermal treatment of **2** in presence of fumaronitrile, leading to cyclopropane **176**. This result can be explained by the formation of a carbene intermediate from the diazo derivative [108], (Scheme 59).

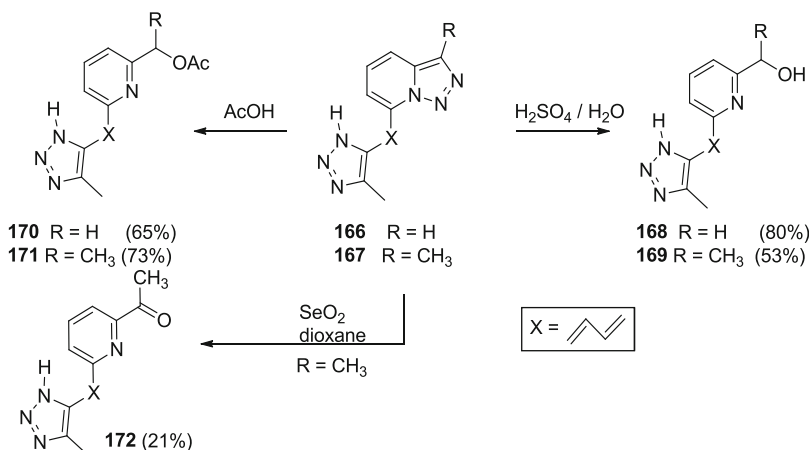
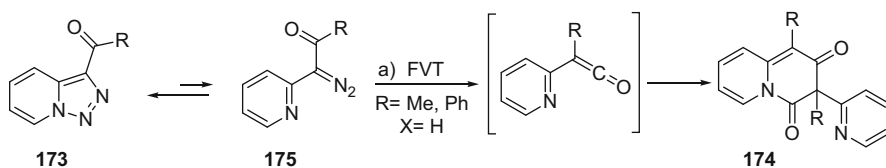
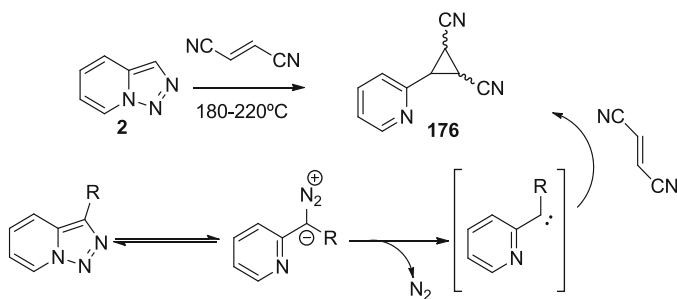
Abarca and Ballesteros also reported of the generation of carbenes in the course of their study on the thermal decomposition of 7-bromotriazolopyridine **177** [109]. The carbene intermediate can be generated by loss of dinitrogen in the corresponding diazo compound before electrophile attack, as indicated in Scheme 59. In this work traces of compound **178** were isolated, and cyclopropanes **179** and **180** were also formed probably by “cyclopropanation” between the carbene and **178** (Scheme 60).

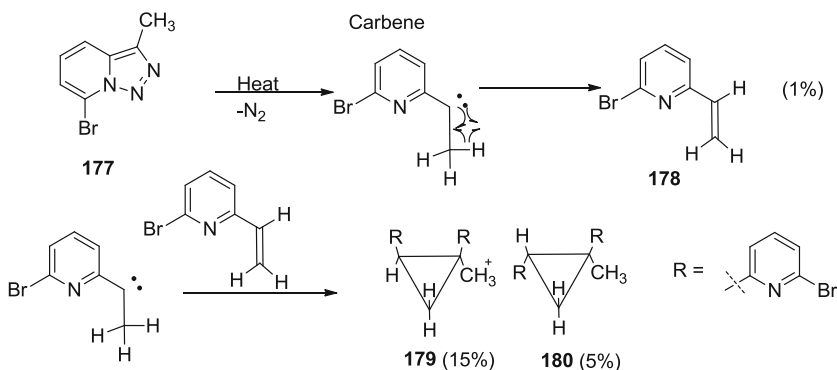
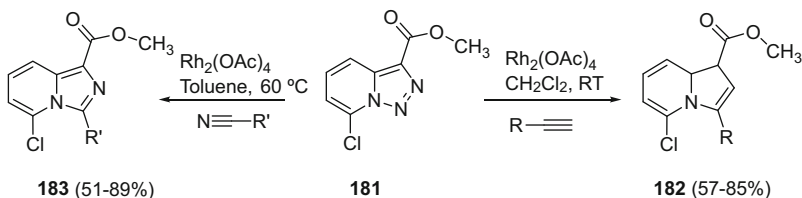
More recently Gevorgyan reported the reaction of 7-chlorotriazolopyridine **181** with rhodium acetate and alkynes or nitriles to afford indolizines **182** and imidazopyridines **183**. Its formation is explained through a diazo intermediate [110] (Scheme 61).

Table 1 Systematic study of the ring-opening reaction in different conditions

Entry	R	R'	XY	Solvent	X	Y	Yield (%)
1	H	H	Cl ₂	CCl ₄	Cl	Cl	67
2	H	H	Br ₂	CCl ₄	Br	Br	75
3	H	H	NBS	CCl ₄	Br	Br	79
4	H	H	Hg(OAc)	AcOH	HgOAc	OAc	60
5	H	5-OCH ₃	Br ₂	CH ₂ Cl ₂	Br	Br	30
6	H	5-OCH ₃	H ₂ SO ₄	H ₂ O	H	OH	78
7	H	7-(<i>p</i> -MeOC ₆ H ₄ CHOH)	Br ₂	CH ₂ Cl ₂	Br	Br	98
8	H	7-(C ₆ H ₅) ₂ CHOH	Br ₂	CH ₂ Cl ₂	Br	Br	76
9	H	H	H ₂ SO ₄	H ₂ O	H	OH	78
10	H	H	AcOH	AcOH	H	OAc	70
11	H	H	SeO ₂	Dioxane	=O Ketone		89
12	CH ₃	H	H ₂ SO ₄	H ₂ O	H	OH	69
13	CH ₃	H	AcOH	AcOH	H	OAc	98
14	CH ₃	H	SeO ₂	Chlorobenzene	=O Ketone		84
15	H	4-CH ₃	Br ₂	CCl ₄	Br	Br	58
16	H	5-CH ₃	Br ₂	CH ₂ Cl ₂	Br	Br	30
17	H	5-CH ₃	H ₂ SO ₄	H ₂ O	H	OH	80
18	H	6-CH ₃	AcOH	AcOH	H	OAc	98
19	H	7-CH ₃	SeO ₂	Dioxane	=O Ketone		<10
20	H	7-CH ₃	SeO ₂	Xylene	=O Ketone		100
21	CONEt ₂	H	H ₂ SO ₄	H ₂ O	H	OH	70
22	CONEt ₂	H	AcOH	AcOH	H	OAc	73
23	CONEt ₂	H	SeO ₂	Xylene	=O Ketone		80
24	H	7-CH ₂ OH	SeO ₂	Xylene	=O Ketone		50
25	H	7-O CH ₃	H ₂ SO ₄	H ₂ O	H	OH	80
26	H	7-O CH ₃	SeO ₂	Chlorobenzene	=O Ketone		60
27	CH ₃	7-(<i>p</i> -anysol)	SeO ₂	Chlorobenzene	=O Ketone		70
28	CH ₃	7-piperidinyl	AcOH	AcOH	H	OAc	75

**Scheme 56** Triazole ring-opening reaction with bromine or iodine

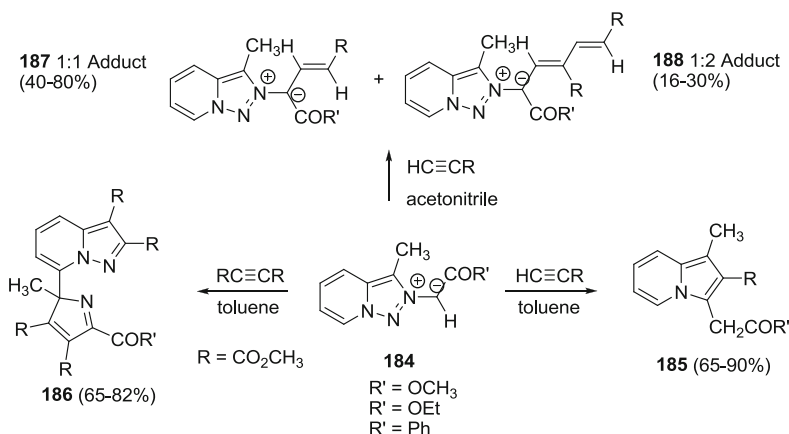
Scheme 57 Triazole ring-opening reactions of **166** and **167**Scheme 58 Diazo compound behaviour of **173**Scheme 59 Cyclopropane formation from **2**

**Scheme 60** Cyclopropane formation from **177****Scheme 61** Rhodium mediated **181** decomposition through a diazo intermediate

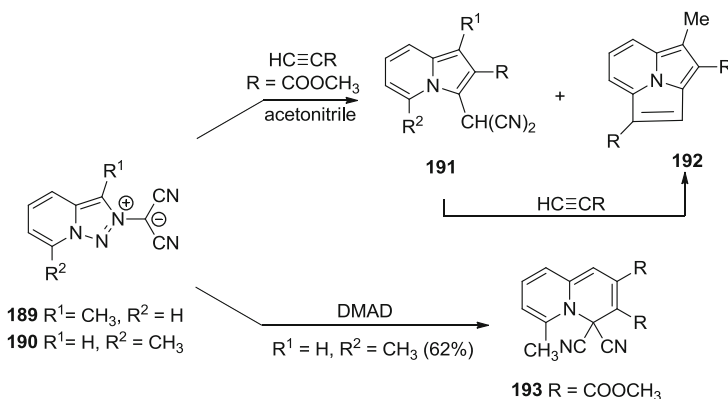
There are also some examples of triazole opening reaction with triazolo-pyridinium ylides. Initially, these experiments were performed with [1,2,3] triazolo[1,5-*a*]pyridinium ylide **184** and acetylenic esters [111–114]. The authors found out that these reactions were extremely solvent polarity dependent and the results could vary according to the acetylenic ester (Scheme 62).

When the synthesis was performed in toluene with methyl propiolate, indolizines **185** were obtained, providing a new way to synthesize this heterocycle [113]. When dimethyl acetylenedicarboxylate (DMAD) was used as dipolarophile in toluene, pyrazolo[1,5-*a*]pyridines **186** were obtained after the addition of two molecules of DMAD. In both cases cleavage of the N²–N³ bond occurred, leading to the triazole ring opening, and a 1,3-dipolar cycloaddition was observed. The structure of these compounds was confirmed by single X-ray [112]. However, when acetonitrile was used as solvent, the reaction of the ylides **184** with methyl propiolate gives in each case two products characterized as 1:1 **187** and 1:2 **188** adducts, with ylide structure and without triazole ring opening.

2-Dicyanomethyl-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **189** and 2-dicyanomethyl-7-methyl-[1,2,3]triazolo[1,5-*a*]pyridinium ylide **190** were also studied. The reactivity of these compounds towards acetylenic esters is different depending on the dipolarophile [115], but always produces the triazole ring-opening reaction with loss of nitrogen. 3-Methylated (R¹=CH₃, R²=H) ylide **189** reacts with methyl propiolate in acetonitrile as solvent to provide indolizine



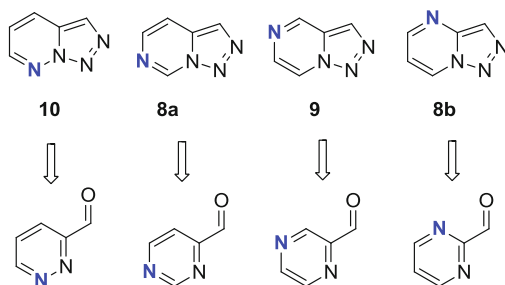
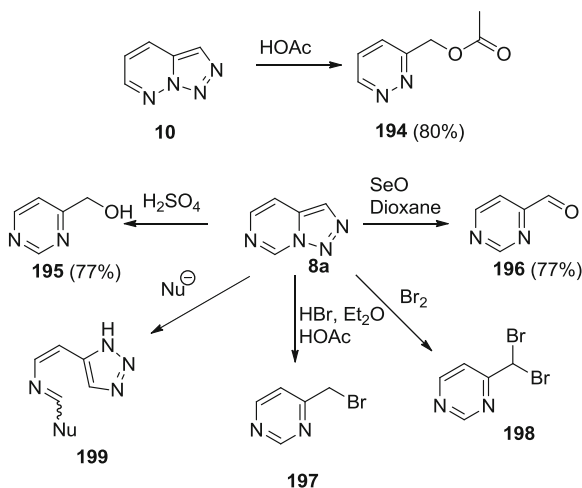
Scheme 62 Triazole ring-opening reaction of ylide **184**

Scheme 63 Ring-opening reactions of **189** and **190**

191 and cyclizine **192**. The reaction performed with the 7-methylated ($R^1=H$, $R^2=CH_3$) ylide **190** provided exclusively the indolizine. 7-Methylated ylide reacted with DMAD to afford 4*H*-4,4-dicyan-2,3-dimethoxycarbonyl-6-methylquinolizine **193** (Scheme 63).

4.4 Reactivity of Triazolodiazines

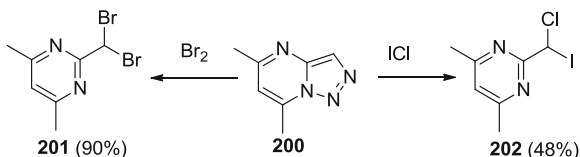
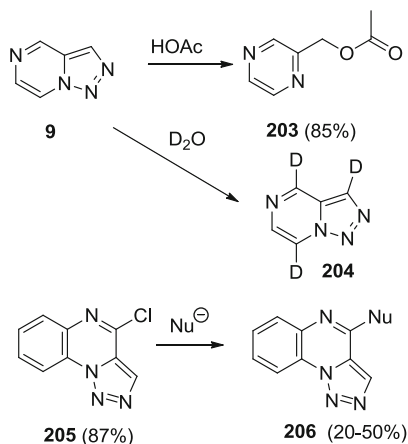
Triazolodiazines represent a less explored family. These compounds are depicted in Scheme 64. In all cases those compounds are obtained by hydrazine/oxidation methodology of the corresponding aldehyde [70, 73]. Despite of not being

Scheme 64 Four nitrogen atom-containing molecules**Scheme 65** Ring-opening reactions on **10** and **8a**

extensively studied from a chemical point of view, many of these structures are evaluated in pharmacological studies.

The presence of the two nitrogen atoms in the six-membered ring induces instability of these systems which are, contrary to almost all of the previous examples, water sensitive. For compound **10** only ring-opening reaction with acetic acid has been reported yielding to acetate **194** [73]. Triazolo[1,5-*c*]pyrimidine **8a** has been extensively studied by Abarca and Jones and behaves similar to triazolo-pyridine **2** [116]. The compound **8a** of acid leads to a ring-opening reaction affording alcohol **195** with H₂SO₄ and ketone **196** with selenium dioxide. Monohalogenation can be achieved with HBr, leading to compound **197**. Jones reported also on the dehalogenation of this molecule with molecular bromine, affording compound **198** [80]. However, in these reactions the presence of a large amount of side products is reported. This has been associated to the instability of these compounds. Indeed, the presence of nucleophiles induces the ring opening of the pyrimidine moiety, leading to triazoles **199** [116] (Scheme 65).

The reactivity of compound **8b** has not been studied; it is only known that dimethyl derivative **200** undergoes ring-opening reaction with bromine, leading

Scheme 66 Reactivity of **200****Scheme 67** Reactivity of **9** and **205**

to compound **201**. In a similar way, when **200** is treated with ICl , halogenated compound **202** is obtained in moderate yield [117] (Scheme 66).

The reaction of pyrazine **9** with acetic acid has also been reported yielding compound **203** in good yield [73]. Despite not being deeply studied, Wentrup reported on the deuteration of this compound with D_2O [91], being able to introduce 3 deuterium atoms (**204**). Of this particular structure, more conjugated analogues, like compound **205**, have been reported [118]. Compound **205** reacts with nucleophiles in moderate yields affording **206** [119] (Scheme 67).

5 Applications of Fused 1,2,3-Triazoles

5.1 Benzotriazole Applications

Benzotriazoles resist hot sulphuric acid or melted KOH treatment; even strong oxidants or reductants (KMnO_4 , LiAlH_4) do not affect this system. Taking into consideration that benzotriazole is relatively cheap and stable up to 400°C , several applications have been reported in different fields.

5.1.1 Organic Synthesis

Katritzky is the main researcher on the application of these compounds in organic synthesis [32]. Several reviews, patents and research articles are reported in the literature just concerning its application in organic synthesis [120–122]. The key point of benzotriazole is that it can be easily introduced into different molecules by means of different reactions. Substitution [32], addition or even three-component reactions had been reported for this purpose. Once **Bt** is attached to a molecule, it can be used under different approaches: as leaving group [123, 124], *ortho*-directing group [125], as cation stabilizer [67], radical precursor [126], etc. Today more than 1,000 publications employ benzotriazoles as a synthetic tool. Schematic examples about the use of **Bt** in organic synthesis are shown in Fig. 6.

In this field it is important to stress the utility of some benzotriazoles in peptide synthesis [127] (Fig. 7). The compounds used in this synthesis are derivatives of hydroxy triazoles **18** [15, 128]. Compounds **207**, **208** and **209** are commercially available and largely employed for amide bond formation with a high degree of racemization suppression [129–131].

5.1.2 Medicinal Applications

The benzotriazole structure (5+6 aromatic rings) displays similarities with the natural bases adenine and guanine (Fig. 8). For this reason it is not surprising that it is considered as a preferential scaffold in pharmaceutical chemistry as long as it allows subsequent derivatization. In particular pyrimidine derivatives tend to be employed [132–134].

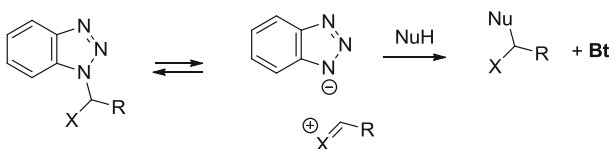
5.1.3 Coordination Chemistry and Metal Organic Frameworks

Benzotriazole and its derivatives had also been applied in coordination chemistry and metal organic frameworks [135–138], in particular, carboxylic derivatives **73** [139] or even more complex molecules **214** [137] (Fig. 9). The particular arrangement of the nitrogen atoms allows coordination with different angles; thus coordination polymers and metal organic frameworks have been obtained. Although this is not the most common nitrogenated ligand employed, its reports reveal particular features that are difficult to obtain with other compounds. Furthermore, these structures are stable.

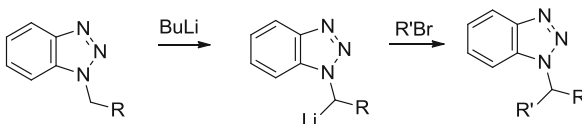
5.1.4 Photostabilizers, Photographic Application and Sensors

Hydroxyphenylbenzotriazole **215** [140, 141] has been used as photostabilizer of polymers. With the addition of this compound, their stability towards light

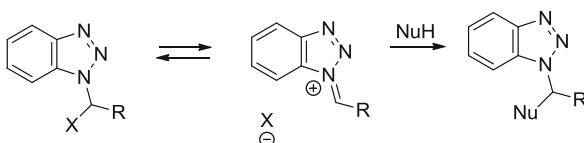
i) **Bt** as leaving group:



ii) **Bt** as proton activator:



iii) **Bt** as cation stabilizer:



vi) **Bt** as anion or radical precursor:

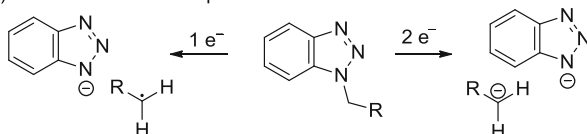


Fig. 6 Benzotriazole in organic synthesis

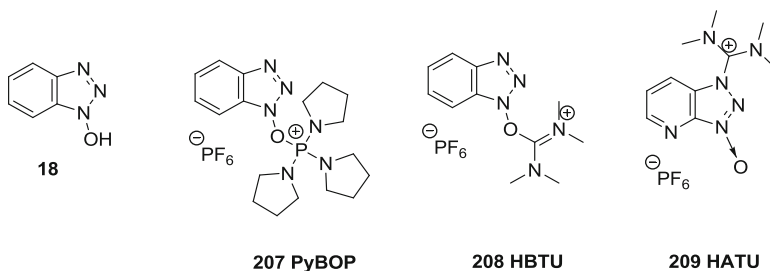
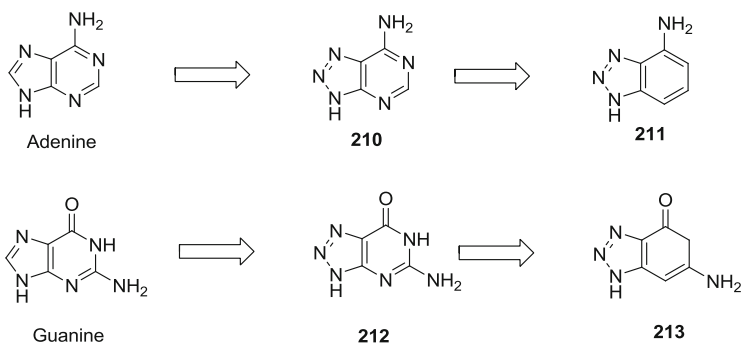
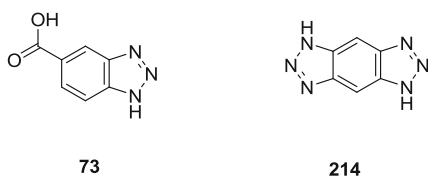
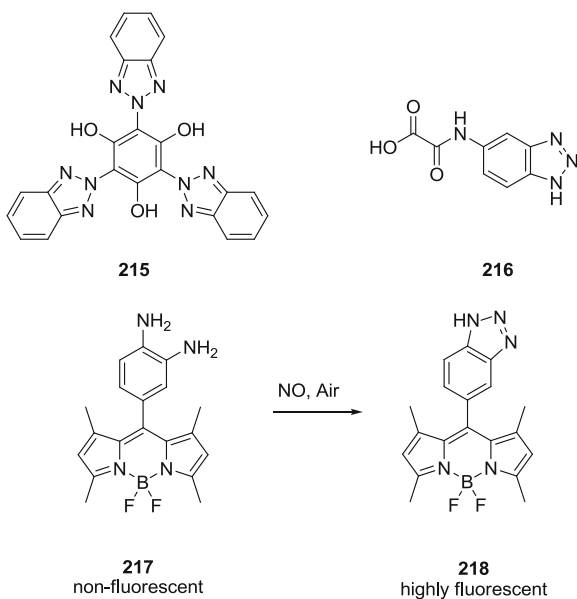


Fig. 7 Benzotriazole-based peptide coupling reagents

increases. In a similar way, compound **216** is employed as a fog inhibitor in the processing of silver photographic material [142] (Fig. 10). The particular facility towards the formation of benzotriazole **218** from the ortho-diamine **217** has been employed as a switch on sensor for NO. The initial molecule presents almost zero emission, but when NO is in the atmosphere, the formation of the benzotriazole ring in **218** leads to a strong emission [143].

**Fig. 8** Analogy between benzotriazole **Bt** and pyrimidinic bases**Fig. 9** Benzotriazole-based ligands employed for the preparation of metal organic frameworks**Fig. 10** Benzotriazole-based compounds as photostabilizers and sensors

5.1.5 Copper Conservation

Benzotriazole has been reported as a copper corrosion inhibitor. Indeed copper and copper alloys are treated with a benzotriazole solution [144, 145]. This method has also been applied for brass, steel, cast iron or aluminium to prevent corrosion [146].

5.2 *Applications of Triazolopyridines with Nitrogen as Bridgehead Atom*

Their reactivity has been shown to be a powerful tool to get access to extremely important compounds in many different yields.

5.2.1 Organic Synthesis

Synthesis of 2,6-Asymmetrically Disubstituted Pyridines and Quinolines

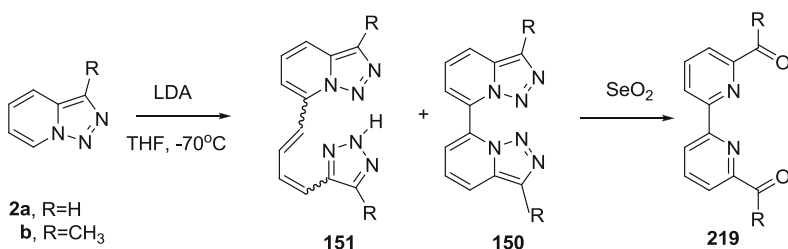
The triazole ring has been employed as an activating and protecting group of 2 aldehyde/ketone pyridines or quinolone. The combination of the triazole ring formation, lithiation, trapping with electrophiles and ring-opening reactions is a powerful strategy to prepare 2,6-asymmetrically disubstituted pyridines or 2,8-asymmetrically disubstituted quinolines. These kinds of molecules are difficult to obtain by other procedures. However, by means of the triazolopyridine chemistry, several compounds have been obtained [80, 82, 100, 147].

A New Route to 2,2'-Bipyridines

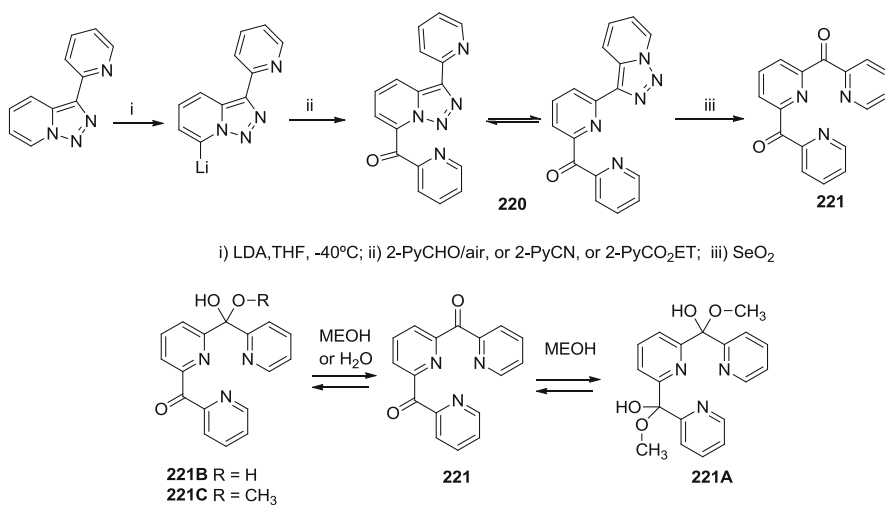
As has been described, the usual reaction between triazolopyridines and lithium reagents at -40°C gives a 7-lithio derivative that can be trapped by electrophiles [80, 147]. This reaction is temperature dependent, and at -70°C in THF as solvent, a new reaction occurs, giving two products, the 7,7'-bitriazolopyridine **150** and the butadiene **151** [82] (see Scheme 48). Like all simple triazolopyridines, bitriazolopyridines **150** react with electrophiles to produce 2,2'-bipyridines **219** (Scheme 68). With these reactions, a general route to 2,2'-bipyridines has been discovered with a variety of substituents in the 6 and 6' positions [82]. These compounds have use in supramolecular chemistry because of their great complexing power for metal ions, and, in particular, 2,2'-disubstituted-6,6'-bipyridines are useful building blocks for oligo-bipyridines, which spontaneously form helical metal complexes [148].

Synthesis of Pyridylcarbonylpyridines

Pyridyl carbonyl pyridyl triazolopyridine **220** is obtained from 3-(2-pyridyl)-triazolopyridine by the typical reaction of lithiation and trapping the lithio



Scheme 68 New synthesis of bipyridines



Scheme 69 Synthesis of bis-(pyridylcarbonyl)pyridine

derivative by 2-PyCHO/air or 2-PyCO₂Et or 2-PyCN. Its triazole ring-opening reaction with SeO₂ formed a bis-pyridylcarbonyl-pyridine **221** [149] (Scheme 69). This compound undergoes hydration or reaction with methanol, leading to compounds **221A**, **221B** and **221C**.

The discovery of this synthesis of compound **221**, using triazolopyridines as building blocks, has been the beginning of a new study looking for new polynitrogenated potential helicing ligands or coordination supramolecular compounds from triazolopyridines with potential magnetic or photochemical properties [150]. The aim of this study was the synthesis of oligopyridylcarbonylpyridines **222** and related compounds. In Fig. 11 there are some examples of the synthesized compounds with this methodology in different conditions [149–152].

Pyridylcarbonylpyridine (PyCOPyCOPy) **221** is a ligand very often used in coordination chemistry to form clusters or helicates with different structures and very interesting magnetic properties. Figure 12 shows the molecular formula of some examples synthesized from **221** and with application in these fields.

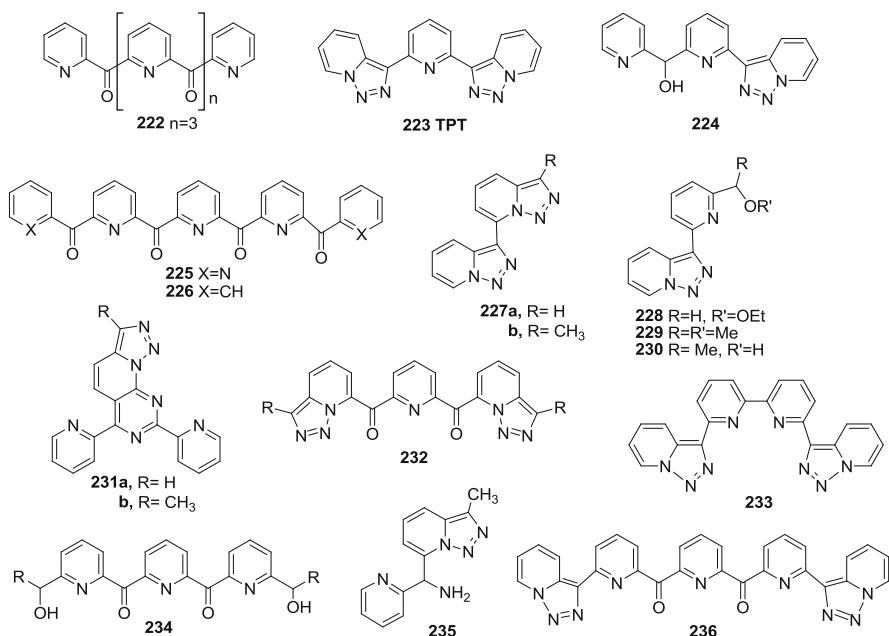


Fig. 11 Oligopyridylcarbonylpyridines and related compounds

Complexes with silver **237** and **238** and copper **239** and **240** [153] and with iron **241–244** [154], the first icosanuclear Co cluster exhibiting superparamagnetic relaxation **245** [155], an *S*-shaped pentanuclear Cu^{II} cluster **246** [156], clusters of Cu^{II}_4 **247** and Co^{II}_4 **248** with ferromagnetic interactions [157], a Ni^{II}_5 cluster **249** with a $S = 5$ ground state exhibiting slow magnetic relaxation and a high spin-reversal barrier have been described [158]; complexes **250–252** (Cu^{II}_4 , Co^{II}_4 and Ni^{II}_6) are also synthesized in the presence of sodium azide with very interesting ferromagnetic intramolecular interactions [159]. Structural, magnetic and spectroscopic studies have been done with **253** (Fe^{III}) [160]. Isomorphous replacement of M^{II} ions in M^{II} - Gd^{II} dimers **254** ($M^{II}=Cu^{II}$ (a), Mn^{II} (b), Ni^{II} (c), Co^{II} (d), Zn^{II} (e) [161], Fe^{II} (f) [162]) has been studied; magnetic susceptibility measures indicate a ferromagnetic interaction for (a), antiferromagnetic for (b–e) and weakly ferromagnetic for (f).

There is a second-generation family of ligands derived from metal ion-assisted reactivity of di-2,6-(2-pyridylcarbonyl)pyridine **221**. A $Mn^{II/III}_4$ rhombus was synthesized by nucleophilic attack of the carbanion $^-CH_2COCH_3$ at the carbonyl carbon atoms of $(py)CO(py)CO(py)$, in the presence of Mn^{n+} ions under basic conditions; the cationic cluster $[Mn_4(OH)_2(L)_2(H_2O)_2](ClO_4)_4$ **255**, where L^{2-} is the $(py)C(CH_2COCH_3)(O^-)(py)C(CH_2COCH_3)(O^-)(py)$ dianion, was synthesized and characterized [163]. Complex **255** is antiferromagnetically coupled with an unusual $S = 2$ ground state resulting from spin frustration effects within the triangular Mn_3 subunits of the cluster.

- 237** $[\{\text{Ag}(\mathbf{121})\}(\text{ClO}_4)]_\infty$
238 $[\{\text{Ag}(\mathbf{121})(\text{NO}_3)\} \cdot \text{CH}_3\text{CN}]_\infty$
239 $[\text{Cu}(\mathbf{121B})]_2(\text{BF}_4)_2 \cdot 2\text{H}_2\text{O}$
240 $[\text{Cu}(\mathbf{121C})]_2(\text{ClO}_4)_2 \cdot 2\text{H}_2\text{O}$
241 $[\text{Fe}_3(\mathbf{121A})_2(\mu\text{-OCH}_3)_2\text{Cl}_2] (\text{FeCl}_4) \cdot \text{H}_2\text{O}$
242 $\text{Fe}(\mathbf{121B})\text{Cl}_2 \cdot \text{H}_2\text{O}$
243 $\text{Fe}(\mathbf{121B})\text{Cl}_2 \cdot \text{THF}$
244 $\text{Fe}(\mathbf{121C})\text{Cl}_2 \cdot \text{THF}$
245 $[\text{Co}_{20}(\mu_3\text{-OH})_6(\text{O}_2\text{CMe})_4(\mu_2\text{-O}_2\text{CMe})_{12}(\mu_3\text{-O}_2\text{CMe})_6(\text{HL})_4(\text{DMF})_2] \cdot 2\text{H}_2\text{O} \cdot 1.6\text{DMF}$, where $\text{HL}^{3-} = \text{pyC}(\text{O})(\text{OH})\text{pyCO}_2\text{py}^{3-}$.
246 $[\text{Cu}_5(\text{O}_2\text{CMe})_6\{\text{pyC}(\text{O})(\text{OH})\text{pyC}(\text{O})(\text{OH})\text{py}\}_2]$
247 $[\text{Cu}_4\{\text{pyC}(\text{O})_2\text{pyC}(\text{O})(\text{OEt})\text{py}\}(\text{O}_2\text{CMe})_5(\text{EtOH})_2]$
248 $[\text{Co}_4\{\text{pyC}(\text{O})(\text{OMe})\text{pyC}(\text{O})(\text{OMe})\text{py}\}_2(\text{O}_2\text{CMe})_2(\text{N}_3)_2]$
249 $[\text{Ni}_5\{\text{pyCOPyC}(\text{O})(\text{OMe})\text{py}\}_2(\text{O}_2\text{CMe})_4(\text{N}_3)_4(\text{MeOH})_2] \cdot 2.6\text{MeOH} \cdot 2.6\text{H}_2\text{O}$
250 $[\text{Cu}_4(\text{N}_3)_2\{\text{pyC}(\text{OMe})(\text{O})\text{pyC}(\text{OMe})(\text{O})\text{py}\}_2(\text{MeOH})_2] (\text{ClO}_4) \cdot 2\text{MeOH}$
251 $[\text{Co}_4(\text{N}_3)_2(\text{NO}_3)\{\text{pyC}(\text{OMe})(\text{O})\text{pyC}(\text{OMe})(\text{O})\text{py}\}_2] \cdot 0.5\text{MeOH}$
252 $[\text{Ni}_6(\text{CO}_3)(\text{N}_3)_6\{\text{pyCOPyC}(\text{O})(\text{OMe})\text{py}\}_3(\text{MeOH})_2(\text{H}_2\text{O})] - [\text{Ni}_6(\text{CO}_3)(\text{N}_3)_6\{\text{pyCOPyC}(\text{O})(\text{OMe})\text{py}\}_3(\text{MeOH})_3] (\text{ClO}_4)_2 \cdot 1.8\text{MeOH}$
253 $[\text{Fe}_2\{\text{pyCO}(\text{OMe})\text{pyCO}(\text{OMe})\text{py}\}_2(\text{MeO})_2] (\text{ClO}_4)_2 \cdot \text{MeOH}$
254 $[\text{M}^{\text{II}}\text{Gd}^{\text{II}}\{\text{pyCO}(\text{OEt})\text{pyC}(\text{OH})(\text{OEt})\text{py}\}_3(\text{ClO}_4)_2 \cdot \text{EtOH}]$ [$\text{M}^{\text{II}} = \text{Cu}^{\text{II}}$ (a), Mn^{II} (b), Ni^{II} (c), Co^{II} (d), Zn^{II} (e), Fe^{II} (f)].
255 $[\text{Mn}_4(\text{OH})_2(\text{L})_2(\text{H}_2\text{O})_2] (\text{ClO}_4)_4$, where L^{2-} is the $\text{pyC}(\text{CH}_2\text{COCH}_3)(\text{O}^-)\text{pyC}(\text{CH}_2\text{COCH}_3)(\text{O}^-)\text{py}$ dianion,

Fig. 12 Molecular formulas of complexes **237–255**

5.2.2 Triazolopyridines as Building Blocks in Supramolecular Chemistry

All triazolopyridines have interesting ligand properties to form polynuclear complexes with different metal ions. These molecules may also have the ability to complex other cationic, neutral or anionic species of biomedical or environmental relevance to form supramolecular compounds, which may have interesting magnetic or fluorescent properties, and could act as luminescent molecular chemosensors.

The following are the preliminary experiments accomplished in supramolecular chemistry, with some of the compounds described in this chapter.

X-ray single-crystal studies and magnetic, photomagnetic and colorimetric measurements of a series of iron(II)-3-(2-pyridyl)-triazolopyridine (**TP**) complexes $[\text{Fe}(\mathbf{TP})_3](\text{BF}_4)_2$ **256**, $[\text{Fe}(\mathbf{TP})_2](\text{NCS})_2 \cdot 2\text{CHCl}_3$ **257**, $[\text{Fe}(\mathbf{TP})_2](\text{NCS})_2 \cdot \text{H}_2\text{O}$ **258** and $[\text{Fe}(\mathbf{TP})_2](\text{NCS})_2$ **259** have been studied and have been characterized as new mononuclear spin crossover compounds [164].

A molecular chemosensor for metal ions, anions and amino acids has been described, the Zn(II) complex of compound **231b** [165]. This system permits the

direct detection of anions without using competitive reactions or dyes. One of the most interesting aspects is the discrimination between nitrite and nitrate anions. The ability of the Zn(II) complex to interact and quantify amino acids has been explored for L-glutamate and L-aspartate.

Triazolopyridine **223 (TPT)** (Fig. 11) possessing fluorescent properties has been studied as molecular chemosensor for Zn(II), nitrite and cyanide anions. The fluorescence behaviour of **TPT** was checked in the presence of the divalent transition metal ions Co^{2+} , Ni^{2+} and Cu^{2+} and of the post-transition metal ions Zn^{2+} , Cd^{2+} and Pb^{2+} . $\text{Zn}(\text{TPT})^{2+}$ 1:1 complex in solution was checked with different monovalent anions (F^- , Cl^- , Br^- , I^- , CN^- , SCN^- , NO_2^- , NO_3^-). In all cases, quenching of the emission was produced. Complex $\text{Zn}(\text{TPT})^{2+}$ is a sensor for anions specially cyanide and nitrite [166].

A tetranuclear complex of Cu(II) with compound **110B** ($\text{R} = 2\text{-PyCO-}$) with magnetic properties has been described; the structure shows a cubane tetrameric complex of copper(II) with the hemiacetalate of the 2-pyridyl-[1,2,3]triazolo[1,5-*a*]pyrid-7-ylmethanone and a S_4 symmetry. The Cu_4O_4 core corresponds to a distorted cubane [167]. The magnetic behaviour of the complex is typical for compounds displaying significant intramolecular antiferromagnetic coupling.

5.2.3 Pharmacological Studies

There are no [1,2,3]triazolo[1,5-*a*]pyridines used as pharmaceutical compounds. This section reports preliminary studies of the pharmacological interest of some triazolopyridines.

Synthesis and Evaluation of 7-Arylhydroxymethyltriazolopyridines as Potential Cardiovascular Agents

7-Arylhydroxymethyltriazolopyridines might be considered as structural analogues of benzyltetrahydroisoquinoline and bisbenzyltetrahydroisoquinoline alkaloids that have the ability to block calcium channels and/or antagonize α_1 -adrenoreceptors, and may have applications in the treatment of cardiovascular disorders. A series of these triazolopyridine derivatives **260** have been synthesized (Fig. 13), and the activity as relaxants of vascular smooth muscle has been tested in isolated aortic rings precontracted by noradrenaline looking for activity as antagonists of the α_1 -adrenoreceptors present in this tissue and stimulated by noradrenaline. The lack of a relaxant action excludes the possibility that these compounds act as α_1 -adrenoreceptors antagonists.

Addition of depolarizing solution to the aortic ring induces a sustained contractile response in the absence of endothelium. In these conditions, opening of voltage-sensitive calcium channels and calcium entry promotes this contractile response. Subsequent addition of these compounds in cumulative concentrations, once the contractile plateau induce by depolarizing solution had been reached, did

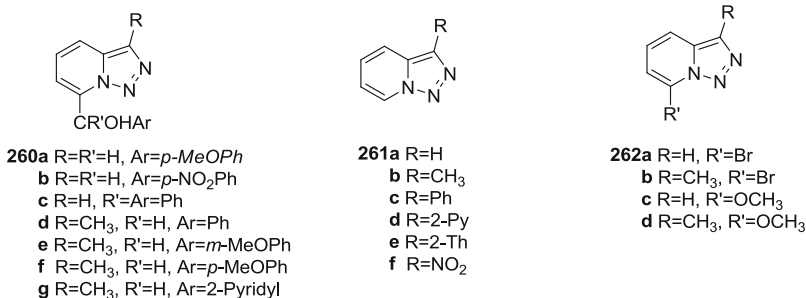


Fig. 13 Triazolopyridines with potential pharmacological activity tested

not modify the tone, thus suggesting that none of the compounds tested can block calcium entry through voltage-dependent calcium channels [168].

Biological Evaluation of [1,2,3]Triazolo[1,5-*a*]pyridines as New Neural Nitric Oxide Synthase Inhibitors

The importance of nitric oxide (NO) as a biological messenger in numerous physiological processes has been demonstrated to a growing extent over the last decades. This molecule is indeed involved in various fundamental functions such as neurotransmission [169], blood pressure and blood flow regulation [170] and platelet aggregation and inflammation [171]. Overproduction of nitric oxide plays a role in a variety of disorders. Nitric oxide is synthesized in several cell types from L-arginine by different isoforms of nitric oxide synthase (NOS).

A series of inhibitors of this enzyme is constituted by heterocycles such as substituted indazoles or imidazoles. The 3- or 7-substituted indazoles are potent nNOS inhibitors [172, 173]. [1,2,3]Triazolo[1,5-*a*]pyridines can be considered as aza-analogues of indazoles, and some studies have been done to test the possibility that the triazolopyridines can be (NO) synthase inhibitors. A number of 3- and 7-substituted triazolopyridines **261** and **262** (Fig. 13) have been synthesized and have been tested [174]. The triazolopyridines evaluated have small activity, and the results indicate that a NH group is necessary for the interaction with the NOS.

References

1. Zhdankin VV ed (2008) Five-membered rings: triazoles, oxadiazoles, thiadiazoles and their fused carbocyclic derivatives In: Katritzky AR, Ramsde CA, Scriven EFV, Taylor RJK (eds) Comprehensive heterocyclic chemistry III and previous collections I and II, vol 5. Elsevier, Oxford
2. Cossy J ed (2008) Bicyclic 5–5 and 5–6 fused ring systems with at least one bridgehead (ring junction) N. In: Katritzky AR, Ramsde CA, Scriven EFV, Taylor RJK (eds) Comprehensive heterocyclic chemistry III and previous collections I and II, vol 11. Elsevier, Oxford

3. Chattaway FD, Orton KJP (1901) The action of acetylchloro- and acetylbromo-aminobenzenes on amines and phenylhydrazine. *J Chem Soc Trans* 79:461
4. Kuhn R, Munzing W (1953) N-Halogen-acrylamide zur Darst, ellung von Tetrszolium-, Triazolium- und 8-Aza-indazolium-Salzen N-Haloacylamides for the preparation of tetrazolium-, triazolium-, and 7a-azaindazolium salts. *Chem Berichte* 86:858
5. Wofford DS, Korkey DM, Russell JG (1982) ^{15}N NMR spectroscopy: prototropic tautomerism of azoles. *J Org Chem* 47:5133
6. Tomás F, Catalán J, Perez P, Elguero J (1994) Influence of lone pair repulsion vs resonance energy on the relative stabilities of molecular structures: a theoretical approach to the equilibrium between 1*H* and 2*H*-benzotriazole tautomers. *J Org Chem* 59:2799
7. Katritzky AR, Yannakopoulou K, Kuzmierkiewicz W, Aurrecoechea JM, Palenik GJ, Koziol AE, Szczesniak M, Skarjune R (1987) The chemistry of N-substituted benzotriazoles. Part 7. The isomeric composition and mechanism of interconversion of some N-(aminomethyl) benzotriazole derivatives. *J Chem Soc Perkin Trans 1* 12:2673
8. Katritzky AR, Bayyuk SI, Rachwal S (1991) An efficient synthesis of ketone enol ethers mediated by N-(1-alkoxyalkyl)benzotriazoles. *Synthesis* 4:279
9. Katritzky AR, Kuzmierkiewicz W, Perumal S (1991) Isomerization of N-[α -(alkylthio)alkyl]- and N-[α -(arylthio)alkyl]benzotriazoles. *Hel Chim Acta* 74:1936
10. Katritzky AR, Ji F-B, Fan W-Q, Gallos JK, Greenhill JV, King RW (1992) Novel Dimroth rearrangements of the benzotriazole system: 4-amino-1-(arylsulfonyl) benzotriazoles to 4-[(Arylsulfonyl)amino]benzotriazoles. *J Org Chem* 57:190
11. De Roos KB, Salemink CA (1971) Deazapurine derivatives. VII. Synthesis of substituted imidazo- and triazolopyridines. *Recueil des Travaux Chimiques des Pays-Bas*. 90:1166
12. Temple C, Smith BH, Montgomery JA (1972) Preparation and properties of some isomeric v-triazolopyridines-1- and 3-deaza-8-azapurines. *J Org Chem* 37:3601
13. Temple C, Smith BH, Montgomery JA (1973) Preparation and properties of isomeric diamino-v-triazolopyridines. 1- and 3-Deaza-2,6-diamino-8-azapurines. *J Org Chem* 38:1095
14. Damschroder RE, Peterson WD (1940) 1,2,3-Benzotriazole. *Org Synt* 20:6
15. Leonard NJ, Golankiewicz K (1969) Thermolysis of substituted 1-acetoxy benzotriazoles. Carbon-to-oxygen migration of an alkyl group. *J Org Chem* 34:359
16. Vaughan JR Jr, Krapcho J, English JP (1949) Triazolo- and imidazopyridines. *J Am Chem Soc* 71:1885
17. Patel PD, Pater MR, Kocsis B, Kocsis E, Graham SM, Warren AR, Nicholins SM, Billack B, Fronczek FR, Talele TT (2010) Design, synthesis and determination of antifungal activity of 5(6)-substituted benzotriazoles. *Eur J Med Chem* 45:2214
18. Torrini I, Zecchini GP, Agrosi F, Paradisi MP (1986) Applications of 1-alkoxycarbonyl- and 1-acyl-v-triazolo[4,5-*b*]pyridines as acylating reagents. *J Heterocycl Chem* 23:1459
19. Holt J, Fiksdahl A (2006) N-acyl and N-alkoxycarbonyl derivatives of 1*H*-1,2,3-triazolo [4,5-*c*]pyridine; preparation and application. *J Heterocycl Chem* 43:417
20. Roblin Jr RO, Lampen, JO, English JP, Cole QP, Vaughan Jr JR (1945) Chemotherapy. VIII. Methionine and purine antagonists and their relation to the sulfonamides. *J Am Chem Soc* 67:290
21. Mitchell G, Rees CW (1987) Cyclo-octa[*def*]carbazole, a new paratropic ring system. *J Chem Soc Perkin Trans 1* 2:403
22. Varma KS, Havaladar F, Nanavati S, Patel B, Fernandes PS (1985) Synthesis of 2*H*-1,2,3-triazolo[4,5-*c*][1,2,4]triazolo[4,3-*a*]pyridines and related systems. *Liebigs Annalen Chem* 9:1922
23. L'abbé G, Vandendriessche A, Weyns N (1988) A new general synthetic method for [1,2,3] triazolo[4,5-*b*]pyridines. *Bull Soc Chim Belg* 97:85
24. Ramanaiah KCV, Stevens ED, Trudell ML, Pagoria PF (2000) Synthesis of 1-substituted [1,2,3]triazolo[4,5-*d*]pyridazines as precursors for novel tetraazapentalene derivatives. *J Heterocycl Chem* 37:1597
25. Ried W, Laoutidis J (1988) Synthesis of new triazolo-annulated 8-azapurines. *Liebigs Annalen Chem* 11:1107

26. Katritzky AR, Kuzmierkiewicz W, Greenhill JV (1991) An improved method for the N-alkylation of benzotriazole and 1,2,4-triazole. *Recueil Travaux Chimiques Pays-Bas* 110:369
27. Carta A, Palomba M, Paglietti G, Mollicotti P, Paglietti B, Cannas S, Zanetti S (2007) [1,2,3] Triazolo[4,5-*h*]quinolones. A new class of potent antitubercular agents against multidrug resistant *Mycobacterium tuberculosis* strains. *Bioorg Med Chem Lett* 17:4791
28. Le Z-G, Chen Z-C, Hu Y, Zheng Q-G (2004) Organic reactions in ionic liquids: a simple highly regioselective or regiospecific substitutions of benzotriazole. *Heterocycles* 63:1077
29. Huynh MHV, Hiskey MA, Chavez DE, Gilardi RD (2005) Tetraazapentalene chemistry: unexpected intramolecular electron rearrangement induced by highly reactive ψ -dinitroso substituents. *Angew Chem Int Ed* 44:7089
30. Maquestiau A, Biemans R, Flammang-Barbieux M, Vilain E (1986) Synthesis of pyridino-benzotetraazapentalenes. *Bull Soc Chim Belg* 95:1107
31. Balachari D, Trudell ML (1997) Synthesis of new dipyridotetraazapentalenes. *Tetrahedron Lett* 38:8607
32. Katritzky AR, Lan X, Yang JZ, Denisko OV (1998) Properties and Synthetic Utility of N-Substituted Benzotriazoles. *Chem Rev* 98:409
33. Hermes ME, Marsh FD (1967) 1-Cyano-1,2,3-triazole- α -diazo-N-cyanoimine tautomers from cyanogen azide and acetylenes. *J Am Chem Soc* 89:4760
34. Katritzky AR, Akue-Gedu R, Vakulenko, AV (2007) C-Cyanation with 1-cyanobenzotriazole. *ARKIVOC* iii:5
35. Hughes TV, Hammond SD, Cava MP (1998) A convenient new synthesis of 1-cyanobenzotriazole and its use as a C-cyanating reagent. *J Org Chem* 63:401
36. Gakh AA, Romaniko SV, Ugrak BI, Fainzilberg AA (1991) N-Fluorination with cesium fluoroxysulfate. *Tetrahedron* 47:7447
37. Niedenzu K, Woodrum KR (1989) Boron-nitrogen compounds. 121. Triazaboles and related triazole derivatives of boron. *Inorg Chem* 28:4022
38. Knight DW, Little PB (2000) 1-Aminobenzotriazole functionalisation using directed metallation: new routes to chromanes and chromenes using intramolecular benzyne trapping by alcohols. *J Chem Soc Perkin Trans 1* 15:2343
39. Efremov DA, Tebby JC, Zavlin PM (1994) The phosphorylation of organic compounds by phosphoric anhydride. Part 2. Phosphorylated azoles. *Phosphorus Sulfur Silicon Relat Elem* 92:167
40. Ruefenacht K (1975) Phosphates and thiophosphates with a heterocyclic substituent. 9. Aza analogs. I. Aza analogs of phthalimide, benzotriazole, and 1,2,3-benzotriazin-4(3H)-one derivatives. *Helvetica Chim Acta* 58:1521
41. Zecchini GP, Torrini I, Paradisi MP (1985) A new route to N2- and N3-substituted-2,3-diaminopyridines. Synthesis of 1- and 3-alkoxycarbonyl-v-triazolo[4,5-*b*]pyridines. *J Heterocycl Chem* 22:313
42. Benko P, Berenyi E, Messmer A, Hajos G, Pallos L (1976) Condensed as-triazines. V. Pyrido [4,3-*e*]-as-triazines. *Acta Chim Acad Scientiarum Hungaricae* 90:405
43. Reid AK, McHugh CJ, Richie G, Graham D (2006) Electron-deficient benzotriazoles for the selective N-acetylation of nucleosides. *Tetrahedron Lett* 47:4201
44. Carta A, Piras S, Boatto G, Paglietti G (2005) 1H,6H-Triazolo[4,5-*e*]benzotriazole 3-oxides and 5,5''-(*Z*)-diazene-1,2-diylbis(2-methyl-2H-1,2,3-benzotriazole) derived from chloronitrobenzotriazoles and hydrazine. *Heterocycles* 65:2471
45. Srinivas D, Ghule VD, Tewari SP, Muralidharan K (2012) Synthesis of amino, azido, nitro, and nitrogen-rich azole substituted derivatives of 1H-benzotriazole for high-energy materials application. *Chem Eur J* 18:15031
46. Graham D, McAnally G (1999) Synthesis of aminobenzotriazoles. *Heterocycl Commun* 5:377

47. Kopanska K, Najda A, Zebrowska J, Chomicz L, Piekarczyk J, Myjak P, Bretner M (2004) Synthesis and activity of 1H-benzimidazole and 1H-benzotriazole derivatives as inhibitors of *Acanthamoeba castellanii*. *Bioorg Med Chem* 12:2617
48. Canada J, Claramunt RM, De Mendoza J, Elguero J (1985) On the possibility of chlorotropy in aromatic azoles: the case of 1,2,3-triazoles and benzotriazoles. *Heterocycles* 23:2225
49. Wright JL, Gregory TF, Kesten SR, Boxer PA, Serpa KA, Meltzer LT, Wise LD, Espitia SA, Konkoy CS, Whittemore ER, Woodward RM (2000) Subtype-selective N-methyl-D-aspartate receptor antagonists: synthesis and biological evaluation of 1-(Heteroarylalkynyl)-4-benzylpiperidines. *J Med Chem* 18:3408
50. Chen H, Wang H (2007) Method for synthesizing benzotriazolecarboxylic acid as copper corrosion inhibitor. *Faming Zhuanli Shenqing Gongkai Shuomingshu* 101029031
51. Katritzky AR, Ji F-B, Fan W-Q, Delprato I (1993) Synthesis of 5,5-Di-(Benzotriazol-5-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione and 5-(Benzotriazol-5-ylmethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione. *Synth Commun* 23:2019
52. Hayashi M, Yamauchi K, Kinoshita M (1976) Esters of phosphorus oxy acids as alkylating agents. IV. N-Alkylation of imidazole and its analogs with alkyl esters of phosphonic and phosphinic acids. *Bull Chem Soc Jpn* 49:283
53. Yutilov YM, Smolyar NN (1996) Radical C-alkylation of 1-substituted 1,2,3-triazolo[4,5-c]pyridines. *Zhurnal Organicheskoi Khimii* 32:1085
54. Yutilov YM, Smolyar NN (1996) Radical C-alkylation of 1-substituted 1,2,3-triazolo[4,5-c]pyridines by tert-butyl alcohol. *Zhurnal Organicheskoi Khimii* 32:1412
55. Svertilova IA, Smolyar NN, Yutilov Y (1996) Synthesis of 4-(arylamino)- and 4-(alkylamino)-1H-imidazo[4,5-c]pyridines and -1,2,3-triazolo[4,5-c]pyridines. *Ukrainskii Khimicheskii Zhurnal (Russian Edition)* 62:64
56. Yutilov YM, Smolyar NN, Astashkina NV (2002) Reduction of imidazo[4,5-c]pyridine and [1,2,3]Triazolo[4,5-c]pyridine derivatives to spinaceamines and 2-azaspinaceamines. *Russian J Org Chem (Translation of Zhurnal Organicheskoi Khimii)* 38:419
57. Plaut GWE (1954) The preparation of 1,5,6-trimethylbenzotriazole and 1-methyl-v-triazole-4,5-dicarboxylic acid. *J Am Chem Soc* 76:5801
58. Burton DE, Lambie AJ, Lane DWJ, Newbold GT, Percival A (1968) Halo-o-phenylenediamines and derived heterocycles. I. Reductive fission of benzotriazoles to o-phenylenediamines. *J Chem Soc [Sect] C Org* 1268
59. Ketari R, Foucaud A (1982) Synthesis of 4-bromo-1-nitropyrzoles and 1-nitrobenzotriazoles (N-nitroazoles). *Synthesis* 10:844
60. Uhde M, Ziegler T (2010) Reaction of N-nitro-benzotriazole with nucleophiles. *Synth Commun* 40:3046
61. Birkett MA, Knight DW, Little PB, Mitchell MB (2000) A new approach to dihydrobenzofurans and dihydrobenzopyrans (chromans) based on the intramolecular trapping by alcohols of benzyne generated from 7-substituted-1-aminobenzotriazoles. *Tetrahedron* 56:1013
62. Campbell CD, Rees CW (1969) Reactive intermediates. III. Oxidation of 1-aminobenzotriazole with oxidants other than lead tetraacetate. *J Chem Soc [Sect] C Org* 752
63. Cresp TM, Wege D (1986) The addition of benzyne to azulene. *Tetrahedron* 42:6713
64. Whitney SE, Rickborn B (1988) Isolation of a 1:1 oxazole-benzyne cycloadduct. An improved method for generating benzyne and a new approach to isobenzofuran. *J Org Chem* 53:5595
65. Whitney SE, Winters M, Rickborn B (1990) Benzyne-Oxazole cycloadducts: isolation and Retro-Diels-Alder reactions. *J Org Chem* 55:929
66. Hart H, Ok D (1986) Synthesis of 1,5-diamino-1,5-dihydrobenzo[1,2-d:4,5-d'] bistriazole (DABT) and its use as a 1,4-benzadiyne equivalent. *J Org Chem* 51:979

67. Katritzky AR, Rachwal S, Rachwal B (1989) Reactions of 1-(α -alkoxyalkyl)- and 1-(α -(aryloxy)alkyl)benzotriazoles with the Grignard reagents. A new and versatile method for the preparation of ethers. *J Org Chem* 54:6022
68. Wang H, Burda C, Persy G, Wirz J (2000) Photochemistry of 1*H*-Benzotriazole in aqueous solution: a phototolerant base. *J Am Chem Soc* 122:5849
69. Blanco F, Alkorta I, Elguero J, Cruz V, Abarca B, Ballesteros R (2008) [1,2,3] Triazolo [1,5-*a*]pyridines. A theoretical (DFT) study of the ring-chain isomerization. *Tetrahedron* 64:11150
70. Tennant G, Vevers RJS (1974) Diazoalkylideneamine-1,2,3-triazole tautomerism in 1,2,3-triazolo[1,5-*a*]pyrimidines at elevated temperatures. *J Chem Soc Chem Commun* 16:671
71. Abarca B, Alkorta I, Ballesteros R, Blanco F, Chadlaoui M, Elguero J, Mojarrad F (2005) 3-(2-pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridines. An experimental and theoretical (DFT) study of the ring-chain isomerization. *Org Biomol Chem* 3:3905
72. Ballesteros-Garrido R, Blanco F, Ballesteros R, Leroux FR, Abarca B, Colobert F, Alkorta I, Elguero J (2009) 3-(Pyridin-2-yl)[1,2,3]triazolo[1,5-*a*]quinoline: a theoretical and experimental analysis of ring-chain isomerisation. *Eur J Org Chem* 33:5765
73. Maury G, Meziane D, Srairi D, Paugan JP, Paugam R (1982) 1,2,3-Triazolo[1,5]azines et autres hétérocycles azotés dérivés d'azine-carboxaldéhydes. *Bull Soc Chim Belgique* 91:153
74. Boyer JH, Borgers R, Wolford LT (1957) The azomethine linkage of pyridine in ring-closure isomerizations. *J Am Chem Soc* 79:678
75. Bower JD, Ramage GR (1957). Heterocyclic systems related to pyrrocoline. II. Preparation of polyazaindenes by dehydrogenative cyclizations. *J Chem Soc* 4506
76. Jones G, Sliskovic DR (1983) The chemistry of the triazolopyridines. *Adv Heterocycl Chem* 34:79
77. Jones G (2002) The chemistry of the triazolopyridines: an update. *Adv Heterocycl Chem* 83:1
78. Abarca B, Ballesteros R, Houari N, Samadi A (1998) The reaction between triazolobenzo-pyridinium and triazolothiazolium ylides with dimethyl acetylenedicarboxylate. *Tetrahedron* 54:3913
79. Boyer JH, Goebel N (1960) The identification of $C_{12}H_8N_4O$, an Oxidation Product from α -Pyridyl Monohydrazone. *J Org Chem* 25:304
80. Jones G, Sliskovic DR (1982) Triazolopyridines. Part 2. Preparation of 7-substituted triazolo [1,5-*a*]pyridines by directed lithiation. *J Chem Soc Perkin Trans 1* 4:967
81. Abarca B, Hayles DJ, Jones G, Sliskovic DR (1983). Triazolopyridines. Part 3. Attempts to introduce substituents into the six-membered ring of 1,2,3-triazolo[1,5-*a*] pyridine. *J Chem Res (Synopses)* 144:1341
82. Jones G, Pitman MA, Lunt E, Lythgoe DJ, Abarca B, Ballesteros R, Elmasnaouy M (1997) Triazolopyridines. 18. Nucleophilic substitution reactions on triazolopyridines; a new route to 2,2'-bipyridines. *Tetrahedron* 53:8257
83. Regitz M (1965) Reactions between active methylene compounds and azides. IX. Synthesis of *v*-triazolo [3,4-*a*]pyridines and 1,2,3-triazoles by diazo group transfer with tosyl azide. *Angew Chem* 77:428
84. Regitz M, Liedhegener A (1966). Reaktionen aktiver Methylenverbindungen mit Aziden, XII. Synthese von Diacyl-diazomethanen durch Diazogruppen-Übertragung. *Chem Berichte* 66:2918
85. Balli H, Loew R, Mueller V, Rempfler H, Sezen-Gezgin A (1978) Azidiniumsalze. 19. Mitteilung [1]. Einführung der Diazogruppe in reaktive Methylenverbindungen mit Azidiniumsalzen. *Helvetica Chim Acta* 61:97
86. Monteiro HJ (1987) Preparation of α -Diazo- β -Ketosulfones by Diazo transfer reaction with an in situ generated azidinium salt. A safe and efficient procedure for the Diazo-transfer reaction in neutral medium. *Synth Commun* 17:983
87. Robbins TF, Qian H, Su X, Hughes RP, Aprahamian I (2013) Cyanide detection using a triazolopyridinium salt. *Org Lett* 15:2386

88. Jones G, Ollivierre H, Fuller LS, Young JH (1991) 1,2,3-triazolo[5,1-b]thiazoles; synthesis and properties. *Tetrahedron* 47:2851
89. Adam R, Ballesteros-Garrido R, Vallcorba O, Abarca B, Ballesteros R, Leroux FR, Colobert F, Amigó JM, Rius J (2013) Synthesis and structural properties of hexaaza[5] helicene containing two [1,2,3]triazolo[1,5-*a*]pyridine moieties. *Tetrahedron Lett* 54:4316
90. Reimlinger H, Lingier WRF, Merényi R (1975) Kondensierte Isochinoline, XIV. Synthese von *v*-Triazolo[5,1-*a*]isochinolininen. *Chem Berichte* 108:3794
91. Wentrup C (1978) [1,2,3]Triazoloazine/(diazomethyl)azine valence tautomers from 5-azinyltetrazoles. *Helvetica Chim Acta* 61:1755
92. Abarca B, Aucejo R, Ballesteros R, Blanco F, García-España E (2006) Synthesis of novel fluorescent 3-aryl- and 3-methyl-7-aryl-[1,2,3]triazolo[1,5-*a*]pyridines by Suzuki cross-coupling reactions. *Tetrahedron Lett* 47:8101
93. Asensio A, Abarca B, Jones G, Hursthouse MB, Abdul Malik KM (1993) Triazolopyridines. 14. Substitution reactions of 7-amino[1,2,3]triazolo[1,5-*a*]pyridines. *Tetrahedron* 49:703
94. Jones G, Richardson CM, Yates PC, Hajos G, Timari G (1993) Theoretical interpretations of some experimental observations in reactions of triazolopyridines and their quaternary salts. *Tetrahedron* 49:4307
95. Davies LS, Jones G (1970) Quinolizines. XIII. Rearrangement of quinolizinium-1-diazonium salts into *v*-triazolo[1,5-*a*]pyridines. *J Chem Res [Sect] C Org* 5:688
96. Abarca B, Gomez-Aldaravi E, Jones G (1984) Triazolopyridines. Part 4. Directed lithiation using 1,2,3-triazolo[1,5-*a*]quinoline. *J Chem Res Synopses* 5:140
97. Ortega N, Tang D-TD, Urban S, Zhao D, Glorius F (2013) Ruthenium–NHC-catalyzed asymmetric hydrogenation of indolizines: access to indolizidine alkaloids. *Angew Chem Int Ed* 52:9500
98. Jones G, Mouat DJ, Pitman MA, Lunt E, Lythgoe DJ (1995) Triazolopyridines. 16 1. lithiation of 3-cyano[1,2,3]triazolo[1,5-*a*]pyridine. *Tetrahedron* 51:10969
99. Abarca B, Ballesteros R, Elmasnaouy M (2002) Triazolopyridines. 21. The stereochemistry of 1-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl-4-(2H-[1,2,3]triazol-4-yl)-1,3-butadienes and triazolo ring opening derivatives. *ARKIVOC* vi:146
100. Ballesteros-Garrido R, Leroux FR, Ballesteros R, Abarca B, Colobert F (2009) The deprotonative metalation of [1,2,3]triazolo[1,5-*a*]quinoline. Synthesis of 8-haloquinolin-2-carboxaldehydes. *Tetrahedron* 65:4410
101. Abarca B, Ballesteros R, Jones G, Mojarrad F (1986) Nucleophilic substitutions on bromotriazolopyridines an improved route to 2,6-disubstituted pyridines and to 1,3-disubstituted isoquinolines. *Tetrahedron Lett* 27:3543
102. Liu S, Sawicki J, Driver TG (2012) Ni-catalyzed alkenylation of triazolopyridines: synthesis of 2,6-disubstituted pyridines. *Org Lett* 14:3744
103. Abarca B, Ballesteros R, Elmasnouy M (1999) Triazolopyridines 20. Hydrogenation reactions. *Tetrahedron* 55:12881
104. Boyer JH, Wolford LT (1958) Alkylation of organic acids with pyridotriazole. *J Am Chem Soc* 80:2741
105. Jones G, Mouat DJ, Tonkinson DJ (1985) Triazolopyridines. Part 6. Ring opening reactions of triazolopyridines. *J Chem Soc Perkin Trans 1* 12:2719
106. Eisbert B, Schade W (1958) Über das Diazoketon, Azi-pyridil. *Chem Ber* 91:1411
107. Plüg C, Kuhn A, Wntrup C (2002) Quinilizine-2,4-diones by reversible dimerisation 2-pyridylketenes. *J Chem Soc Perkin Trans 1* 1366
108. Wentrup C (1974) Thermochemistry of carbene and nitrene rearrangements. *Tetrahedron* 30:1301
109. Abarca B, Ballesteros R, Blanco F (2007) Pyridylcarbene formation by thermal decomposition of 7-bromo-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine under pressure. *ARKIVOC* iv:297
110. Chuprakov S, Hwang FW, Gevorgyan V (2007) Rh-catalyzed transannulation of pyridotriazoles with alkynes and nitrile. *Angew Chem Int Ed* 46:4757

111. Abarca B, Ballesteros R, Mojarrad F, Metni MR, Garcia-Granda S, Perez-Carreno E, Jones G (1991) Triazolopyridines. Part 11. Ylides derived from 2-acylmethyl triazolo pyridinium salts. *Tetrahedron* 47:5277
112. Abarca B, Ballesteros R, Metni MR, Jones G, Ando DJ, Hursthouse MB (1991) A remarkable rearrangement during reaction between triazolopyridinium ylides and dimethyl acetylenedicarboxylate. *Tetrahedron Lett* 32:4977
113. Abarca B, Ballesteros R, Metni MR, Jones G (1992) Triazolopyridines. Part 12. A new synthesis of indolizines from triazolopyridinium ylides. *Heterocycles* 33:203
114. Abarca B, Ballesteros R, Jones G (1993) Triazolopyridines. 15. Reactions between triazolopyridinium ylides and alkenes. *Heterocycles* 35:851
115. Abarca B, Ballesteros R, Muñoz A, Jones G (1996) Triazolopyridines. 17. N2-dicyanomethylides: Synthesis, structure and reactivity with acetylenic dipolarophiles. *Tetrahedron* 52:10519
116. Abarca B, Ballesteros R, Chadlaoui M, Miralles J, Murillo JV, Colonna D (2001) The chemistry of [1,2,3]triazolo[1,5-c]pyrimidine. *Tetrahedron* 57:10111
117. Novinson T, Dea P, Okabe T (1976) Ring opening of 5,7-dimethyl-v-triazolo[1,5-a]pyrimidine by halogenating agents. *J Org Chem* 41:385
118. Vogel M, Lippmann E (1987) Quinoxalines. XXIV. Synthesis of 4-substituted 1,2,3-triazolo [1,5-a]quinoxalines. *J fuer Praktische Chem (Leipzig)* 329:101
119. Vogel M, Lippmann E (1987) Quinoxalines XXV. Reactions of 4-chloro-1,2,3-triazolo [1,5-a]quinoxalines with bases. *Zeitschrift fuer Chem* 27:38
120. Katritzky AR, Rachwal S (2009) Synthesis of heterocycles mediated by benzotriazole. 1. Monocyclic systems. *Chem Rev* 110:1564
121. Katritzky AR, Kuanar M, Slavov S, Hall CD, Karelson M, Kahn I, Dobchev DA (2010) Quantitative correlation of physical and chemical properties with chemical structure: utility for prediction. *Chem Rev* 110:5714
122. Katritzky AR, Huang L, Chahar M, Sakhuja R, Hall CD (2012) The chemistry of N-hydroxyamidoximes, N-aminoamidoximes, and hydrazidines. *Chem Rev* 112:1633
123. Katritzky AR, Avan I, Tala SR (2009) Efficient preparation of aminoxyacyl amides, aminoxy hybrid peptides, and α -aminoxy peptides. *J Org Chem* 74:8690
124. Katritzky AR, El-Gendy BE-DM, Todadze E, Abdel-Fattah AAA (2008) (α -aminoacyl) amino-substituted heterocycles and related compounds. *J Org Chem* 73:5442
125. Katritzky AR, Abdel-Fattah AAA, Gromova AV, Witek R, Steel PJ (2005) α -Nitro ketone synthesis using N-acylbenzotriazoles. *J Org Chem* 70:9211
126. Kaim LE, Meyer C (1996) An unprecedented radical reaction of benzotriazole derivatives. A new efficient method for the generation of iminyl radicals. *J Org Chem* 61:1556
127. Panda SS, Hall CD, Scriven E, Katritzky AR (2013) Aminoacyl benzotriazolides: versatile reagents for the preparation of peptides and their mimetics and conjugates. *Aldrichimica Acta* 46:43
128. Carpino LA (1993) 1-Hydroxy-7-azabenzotriazole. An efficient peptide coupling additive. *J Am Chem Soc* 115:4397
129. Coste J, Le-Nguyen D, Castro B (1990) PyBOP®: a new peptide coupling reagent devoid of toxic by-product. *Tetrahedron Lett* 31:205
130. Carpino LA, Imazumi H, El-Faham A, Ferrer FJ, Zhang C, Lee Y, Foxman BM, Henklein P, Hanay C, Mügge C, Wenschuh H, Klose J, Beyermann M, Bienert M (2002) The Uronium/Guanidinium peptide coupling reagents: finally the true uronium salts. *Angew Chem Int Ed* 41:441
131. Carpino LA, Imazumi H, Foxman BM, Vela MJ, Henklein P, El-Faham A, Klose J, Bienert M (2000) Comparison of the effects of 5- and 6-HOAt on model peptide coupling reactions relative to the cases for the 4- and 7-isomers. *Org Lett* 2:2253
132. Suma BV, Natesh NN, Madhavan V (2011) Benzotriazole in medicinal chemistry: an overview. *J Chem Pharm Res* 3:375

133. Palumbo P, Guarcello A (2010) Bioactive compounds containing benzoxadiazole, benzothiadiazole, benzotriazole. *Curr Bioactive Comp* 6:266
134. Holý A, Dvořáková H, Jindřich J, Masojídková M, Buděšínský M, Balzarini J, Andrei G, De Clercq E (1996) Acyclic nucleotide analogs derived from 8-azapurines: synthesis and antiviral activity. *J Med Chem* 39:4073
135. Aromí G, Barrios LA, Roubeau O, Gamez P (2011) Triazoles and tetrazoles: prime ligands to generate remarkable coordination materials. *Coord Chem Rev* 255:485
136. Shen Y-C, Li Z-J, Cheng J-K, Qin Y-Y, Yao Y-G (2007) Benzotriazole controlled unusual building blocks in two zinc complexes and their fluorescence properties. *Inorg Chem Commun* 10:888
137. Biswas S, Grzywa M, Nayek HP, Dehnen S, Senkovska I, Kaskel S, Volkmer D (2009) A cubic coordination framework constructed from benzobistriazolate ligands and zinc ions having selective gas sorption properties. *Dalton Trans* 33:6487
138. Han Z-B, Lu R-Y, Liang Y-F, Zhou Y-L, Chen Q, Zeng M-H (2011) Mn(II)-based porous metal-organic framework showing metamagnetic properties and high hydrogen adsorption at low pressure. *Inorg Chem* 51:674
139. Xiao J, Wu Y, Li M, Liu B-Y, Huang X-C, Li D (2013) Crystalline structural intermediates of a breathing metal-organic framework that functions as a luminescent sensor and gas reservoir. *Chem Eur J* 19:1891
140. Vogl O, Li S (1983) Di- and tri(benzotriazolyl)trihydroxybenzenes. USA Patent, US 539493
141. Stoeber L, Sustic A, Simonsick WJ, Vogl O (2000) Functional polymers 64. Potassium ionisation of desorbed species (K+IDS) of 2(2-hydroxyphenyl)2H-benzotriazoles. *J Macromol Sci A* 37:1269
142. Ohashi M, Horii S (1990) Method for processing photographic material containing antifoggant. Japan Patent US 4,920,043
143. Gabe Y, Urano Y, Kikuchi K, Kojima H, Nagano T (2004) Highly sensitive fluorescence probes for nitric oxide based on boron dipyrromethene chromophore rational design of potentially useful bioimaging fluorescence probe. *J Am Chem Soc* 126:3357
144. MacLeod ID (1987) Conservation of corroded copper alloys: a comparison of new and traditional methods for removing chloride ions. *Stud Conserv* 32:25
145. Sease C (1978) Benzotriazole: a review for conservators. *Stud Conserv* 23:76
146. Madsen HB (1967) A preliminary note on the use of benzotriazole for stabilizing bronze objects, 12/4 1967. *Stud Conserv* 12:163
147. Jones G, Sliskovik DR (1980) [1,2,3]Triazolo[1,5-a]pyridine-A synthon for 6-disubstituted pyridine-2-carboxaldehydes. *Tetrahedron Lett* 21:4529
148. Lehn JM (1995) Supramolecular chemistry. VCH, Weinheim (Bundessrepublik Deutschland)
149. Abarca B, Ballesteros R, Elmasnaouy M (1998) A facile route to potential helically ligands. *Tetrahedron* 54:15287
150. Abarca B, Ballesteros R, Chadlaoui M (2004) Triazolopyridines. Part 24: new polynitrogenated potential helically ligands. *Tetrahedron* 60:5785
151. Abarca B, Aucejo R, Ballesteros R, Chadlaoui M, García-España E, Ramírez de Arellano C (2005) X-ray characterization of 3-methyl-6,8-di(2-pyridyl)-[1,2,3]triazolo [5',1':6,1]pyrido [2,3-d]pyrimidine. *ARKIVOC* xiv:71
152. Abarca B, Ballesteros R, Chadlaoui M (2008) Synthesis of novel polypyridyl carbonyl-pyridines from triazolopyridines. Building blocks in supramolecular chemistry. *ARKIVOC* vii:73
153. Chen XD, Mak TCW (2005) Molecular and supramolecular architectures of silver(I) and copper(I) complexes of 2,6-pyridinediylbis(2-pyridinyl)methanone. *J Mol Struct* 748:183
154. Chen XD, Du M, He F, Chen XM, Mak TCW (2005) Molecular and supramolecular architectures of silver(I) and copper(I) complexes of 2,6-pyridinediylbis(2-pyridinyl)methanone. *Polyhedron* 1047

155. Boudalis AK, Raptopoulou CP, Abarca B, Ballesteros R, Chadlaoui M, Tuchages JP, Terzis A (2006) Co^{II} Chemistry of 2,6-Bis(2-pyridylcarbonyl)-pyridine: an icosanuclear co cluster exhibiting superparamagnetic relaxation. *Ange Chem Int Ed* 45:432
156. Boudalis AK, Raptopoulou CP, Psycharis V, Sanakis Y, Abarca B, Ballesteros R, Chadlaoui M (2007) An "S"-shaped pentanuclear Cu^{II} cluster derived from the metal-assisted hydrolysis of pyCOPyCOPy: structural, magnetic and spectroscopic studies. *Dalton Trans* 36:3582
157. Boudalis AK, Raptopoulou CP, Psycharis V, Abarca B, Ballesteros R (2008) Ferromagnetism in Cu^{II}₄ and Co^{II}₄ complexes derived from metal-assisted solvolysis of Di-2,6-(2-pyridylcarbonyl)pyridine: synthesis, structures, and magnetic properties. *Eur J Inorg Chem* 3796
158. Boudalis AK, Pissas M, Raptopoulou CP, Psycharis V, Abarca B, Ballesteros R (2008) Slow magnetic relaxation of a ferromagnetic Ni cluster with an S = 5 ground state. *Inorg Chem* 47:10674
159. Georgopoulou AN, Raptopoulou CP, Psycharis V, Ballesteros R, Abarca B, Boudalis AK (2009) Ferromagnetic Cu, Co, and Ni azido complexes derived from metal-assisted methanolysis of Di-2,6-(2-pyridylcarbonyl)pyridine. *Inorg Chem* 48:3167
160. Georgopoulou AN, Adam R, Sanakis Y, Raptopoulou CP, Psycharis V, Ballesteros R, Abarca B, Boudalis AK (2009) A diferric complex from metal-assisted methanolysis of di-2,6-(2-pyridylcarbonyl)pyridine: structural, magnetic and spectroscopic (Mössbauer, EPR) study. *Polyhedron* 28:3251, Corrigendum (2010) *Polyhedron* 29:1189
161. Georgopoulou AN, Adam R, Raptopoulou CP, Psycharis V, Ballesteros R, Abarca B, Boudalis AK (2010) Isomorphous replacement of MII ions in MII- GdIII dimers (MII = CuII, MnII, NiII, CoII, ZnII): magnetic studies of the products. *Dalton Trans* 39:5020
162. Georgopoulou AN, Adam R, Raptopoulou CP, Psycharis V, Ballesteros R, Abarca B, Boudalis AK (2011) Expanding the 3d-4f heterometallic chemistry of the (py)₂CO and pyCOPyCOPy ligands: structural, magnetic and Mössbauer spectroscopic studies of two Fe^{II}-Gd^{III} complexes. *Dalton Trans* 40:8199
163. Stamatatos TC, Adam R, Raptopoulou CP, Psycharis V, Ballesteros R, Abarca B, Perlepes SP, Boudalis AK (2012) The first member of a second generation family of ligand derived from metal.ion assisted reactivity of di-2,6-(2-pyridylcarbonyl)pyridine: synthesis and characterization of a Mn^{II}₄ rhombus. *Inorg Chem Comm* 15:73
164. Niel V, Gaspar AB, Muñoz MC, Abarca B, Ballesteros R, Real JA (2003) Spin crossover behaviour in the Iron(II)-2-pyridyl[1,2,3]triazolo[1,5-a]pyridine system: X-ray structure, calorimetric, magnetic, and photomagnetic studies. *Inorg Chem* 42:4782
165. Chadlaoui M, Abarca B, Ballesteros R, Ramírez de Arellano C, Aguilar J, Aucejo R, García-España E (2006) Properties of a Triazolopyridine System as a Molecular Chemosensor for Metal Ions, Anions, and Amino Acids. *J Org Chem* 71:9030
166. Ballesteros-Garrido R, Abarca B, Ballesteros R, Ramírez de Arellano C, Leroux FR, Colobert F, García-España E (2009) [1,2,3]Triazolo[1,5-a]pyridine derivatives as molecular chemosensors for zinc(II), nitrite and cyanide anions. *New J Chem* 33:2102
167. Abarca B, Ballesteros R, Chadlaoui M, Ramírez de Arellano C, Real JA (2007) [(Pyridylcarbonyl)-pyridyl]triazolopyridines, useful ligands for the construction of polynuclear coordination compounds- synthesis, crystal structure and magnetic properties of a novel tetranuclear copper(II) cubane. *Eur J Inorg Chem* 4574
168. Abarca B, Ballesteros R, Elmasnaouy M, D'Ocon P, Ivorra MD, Valiente M (2002) Evaluation and synthesis of 7-arylhydroxymethyltriazolopyridines as potential cardiovascular agents. *ARKIVOC* x:9
169. Kiss JP, Vizi ES (2001) Nitric oxide: a novel link between synaptic and nonsynaptic transmission. *Trends Neurosci* 24:211
170. Kadekaro M, Summy-Long JY (2000) Centrally produced nitric oxide and the regulation of body fluid and blood pressure homeostases. *Clin Exp Pharmacol Physiol* 27:450
171. Bredt DS (1999) Endogenous nitric oxide synthesis: Biological functions and pathophysiology. *Free Radic Res* 31:577

172. Schumann P, Collot V, Hommet Y, Gsell W, Dauphin F, Sopkova J, MacKenzie E, Duval D, Boulouard M, Rault S (2001) Inhibition of neuronal nitric oxide synthase by 7-methoxyindazole and related substituted indazoles. *Bioorg Med Chem Lett* 11:1153
173. Tuynman A, Pérollier C, Frapart Y, Schumann P, Collot V, Rault S, Boucher JL (2003) Inhibitory effects and spectral interactions of isomeric methoxyindazoles on recombinant nitric oxide synthases. *Nitric Oxide* 9:86
174. Abarca B, Ballesteros R, Blanco F, Collot V, Rault S, Schumann-Bard P (2003) Pharmacological evaluation of [1,2,3]Triazolo[1,5-*a*]pyridines as new compounds inhibitors of neuronal nitric oxide synthase. XIII Congreso Nacional de la Real Sociedad Española de Química. Terapéutica, Santiago de Compostela (Spain)

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